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Biotechnology: Action and choice in second modernity.

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Introduction

In this project I try to cast a light upon the production and distribution of biological and medical knowledge in the late phase of modernity. I have tried to describe some central developments on the interface of science, medical practice and society and to situate these within broader modern dynamics. Within those dynamics, science and technology are both cause and consequence, made possible through the media of abstract bodies of standardising knowledge.

I have done so by regarding life sciences and technologies from the perspective of social action as interpreted through philosophical hermeneutics. I take this perspective to be important for two reasons. First, science and technology have severe implications, good and bad, for the ways in which we organise society, and for the ways in which we inter-act with each other and the world. Second: knowledge, the abstract medium of science and technology, comes about through concrete interventions carried out in experimental action. Biomedical science and technologies come about through the disciplined isolation of very specific aspects of nature, aspects that can only be cultivated through highly specialised actions on the hands of experts. In that state of affairs lays the origin of a paradox: actions centred on large scale purification of nature's simple elements can only be brought about through what seems to be ever more complex modes of social organisation and through increasing costs and resource allocations to highly specific domains of action. Due to this state of affairs, the isolation and purification of nature's resources may blind us to the wider social issues and interests for which they were brought about in the first place. As we probe deeper into nature, greater social complexity and political and moral dilemmas seem to follow (ecological crisis being the prime example).

These are dilemmas that cannot be solved through the same mechanisms of social organisation as those which created them. The social good or bad resulting from science and technology cannot be assessed through the restricted scope of scientific or technological ways of relating to the world.

As the socio-technological experiments of the life sciences are still young, and as their consequences are so complex and wide-reaching, it is impossible to assess their wider implications with anything approaching a sufficient overview. And, as the "total" consequences get increasingly harder to grasp and evaluate the *need* for doing so increases

inversely. This is, I take it, one main motivation behind the attempts to reclaim the social dimension of science and technology for common sense (as carried out in science and technology studies during the last thirty years). This is also my reason for trying to come to terms with the science and technology of medicine in terms of social action. As the consequences cannot be fully assessed, not to say, predicted, I take one step back and try to analyse *some* of the basic conditions under which action and choice undergo change along with the socialisation of medical technologies and the increasing importance of the life sciences. Because nobody can anticipate or oversee the total consequences of socialised science and technology, the need for developing broad mechanisms and institutions for policy making capable of incorporating a wide scope of views and interests emerges as a pressing matter.

As argued already in 1959 by C. P. Snow, the sharp divide between the cultural and the natural sciences poses a decisive hindrance to that goal. The western production and distribution of knowledge generally takes place along sharply separated spheres of knowing and acting: the natural sciences thrive on the exclusion of any historical, sociological or aesthetic dimension, whereas the cultural and social sciences in general do not concern themselves greatly with the powerful forces of science and technology. The *consequences* of scientific and technological modernisation, of course, do not respect these divisions: the everyday worlds in which we live are deeply embedded within both cultural and technological structures. Hence, as diagnosed by Ulrich Beck: increasingly, the world in which we *think* is not the same as the one in which we *live* (Beck 1993). *Between* those two, we find the worlds in which we act and make judgements, which are constantly challenged by the opposition between thought and reality promoted by the dynamics of modernity.

The project is structured around three action-organising principles: the central dogma of molecular-biology, the legal and political institute of patentability of living organisms, and the ethical and legal institute of patient autonomy.

I have called these principles counterfactual organisers. Centrally, I have used this term to designate the fact that they are rational principles dealing with agency and causality that go beyond the merely experienced. They serve to structure the world not only according to experience, but also according to rationally established principles, and they use these principles also in the projection of future events, i.e. for the sake of policy-making.

In the case of *the central dogma*, the principle in question states the uni-directionality of gene-protein interaction. Once these mechanisms have been sufficiently established, they may serve as basis for the present and future intervention with physiological processes of normality and pathology. Significantly, the central dogma promise to transform the boundary between such previously established categories on a broad basis with implications for the whole of health-care.

In the case of the *patentability of living things*, it is the general assumption that the promotion of commercially viable products in biomedical research will turn out for the better to the economy (industry) and to the health care system in general. The social good to be derived results from the ability of patentability to regulate and promote networks of exchanges of commodities, information and capital, that arise between actors within the new complex of academic-industrial relations.

Last, but not least, we have the principle of patient *autonomy*, promoting an image of the patient as an agent capable of making rational decisions about medical interventions based upon correct information and sound medical advice during the course of the clinical encounter.

Although it is only during the last thirty years or so that these principles have worked their way towards the centre of medicine and health care, they are not at all novel to the modern production of knowledge. Indeed, the notion of physiological function established on secure scientific principles cleansed of unwanted external influences, go right back to thinkers like Galileo, Descartes, Locke and Claude Bernard. The same, we may state, is the case with the notion of the rational agent. Indeed, the ethical notion of rational agency is directly correspondent to that of scientific certainty: ethically responsible action is action carried out on the basis of the best available (scientific) knowledge. The patentability of living things may also be traced back to this period and the establishment of the right to private property, as articulated by John Locke. The new situation, articulated with recourse to Ulrich Beck's theory of reflexive modernisation, is that these principles come together in the organisation of the same issues. This was, until the last thirty or forty years, not the case: scientific knowledge of normality and pathology belonged within the sphere of medicine; patentability belonged

mainly within the sphere of industry, and autonomy was a general principle of the political and legal domains of action.

The text should be regarded as being of an experimental character. As may be seen from the above remarks I have allowed myself of a certain interpretive freedom. When I have done so, it may have been out of a partial discontent with existing theoretical approaches in the field of science and technology, but it may also have been out of initial ignorance of many of the many approaches that there are. When I started on this project I did so from what I had at hand at the moment. Being a PhD student at the *Senter for Vitenskapsteori*[1] in Bergen I found myself between two different theoretical alternatives. On the one hand there was the discourse theoretical approach of my then supervisor Gunnar Skirbekk, placed somewhere on a continuum between Richard Rorty and Karl Otto Apel, and with a strong emphasis on the works of Jürgen Habermas. This approach naturally tends towards political science and the humanities. This leaning was further strengthened by the influences from my second supervisor, Jan Fridthjof Bernt at the faculty of law in Bergen, where he and David Doublet have developed systems theoretical approaches to legal studies (especially Luhmann but also Habermas). On the other hand there were Roger Strand and Ragnar Fjelland, coming from the natural sciences and deploying methods taken more from Science and Technology Studies (STS) and phenomenology[2]. As I started to delve into the matter I came to realise that discourse theoretical or systems theoretical perspectives would be ill suited to describing the peculiarities of the natural sciences and their interactions with society. This influence was further strengthened as Gunnar Skirbekk retired and Roger Strand took over responsibility for supervising the project.

At the same time, however, I felt that the STS approach would lack the abilities of articulating the normative issues involved found in discourse theory especially and political theory and ethics in general. This discontent was strengthened as I also came to take an interest in the discipline of bioethics.

[1] Which in English bears the honourable name of *The centre for the study of the sciences and the humanities*.
[2] It should be noted that although this difference in theoretical approaches exist at the *Senter for Vitenskapsteori* they all co-exist in a harmonious manner, and so there was no problems if somebody should try and somehow mix the approaches.

About this time I got in touch with Ulrich Beck's research group in Munich. This was a lucky strike, as it furthered the impetus to seek out a middle position with regards to the above mentioned approaches. Coming more from hermeneutics myself, but feeling that that field had lagged behind developments in the natural sciences (starting already in the middle of the previous century), I took an interest in the hermeneutic approaches and critiques of Scott Lash and Brian Wynne directed towards the theory of reflexive modernisation. I perceived the critique to be interesting but somehow mis-conceived, and I decided to read Beck's theory as a sort of macro-hermeneutics, in the words of Charles Taylor (in his book on Hegel), a dialectical hermeneutics. During a stay in Munich I also had the opportunity of discussing this approach with Ulrich Beck, who welcomed such an interpretation and encouraged the attempt. This impression remained also during my second stay in Munich which took place towards the end of the project.

At this later stage I had also come to learn about other interesting approaches, significantly that of the Co-production idiom of Sheila Jasanoff and the Social Epistemology of Steve Fuller. Concerning Jasanoff's approach I felt that it already said many of the things I was trying to say, but that my somewhat more philosophical attempt could be worth it anyway. As to Fuller's social epistemology (as far as I have understood it), I found it an interesting counterpoint and correction to STS, but not a substitute for the more case-oriented approach of these studies. Generally, however, it is my contention that hermeneutics should not be opposed to these approaches, but rather complementary to them.

The thesis consists of ten chapters. In the first chapter I introduce the hermeneutic conception of Being-in-the-world as an alternative to the modernist anthropology that has been dominant since the times of Galileo and Descartes. I furthermore interpret Heidegger's philosophy as a hermeneutic of action and I describe some elements of Heidegger's philosophy of technology that will be used later, centrally that of material agency as a standing-reserve (*Bestand*). Following that I continue by giving an overview of relevant theories of science and society. I address some of the developments within science and technology studies (particularly those dealing with the laboratory), arguing the positive sides these approaches have over traditional philosophy of science (epistemology). Centrally, we need more sociologically oriented understandings, and we need frameworks that do not presuppose rigid divisions between culture and nature. However, I also argue that these disciplines may be lacking in institutional and normative aspects, and I suggest that the use of Ulrich Beck's theory may prove one good

intake to these other dimensions. Because there is no explicit theory of action to be found in Beck, nor a theory of experimental action, in chapter three I turn towards the task of developing such a framework. For that purpose I use Rheinberger's account of epistemic things as a supplement to the Heideggerian philosophy of technology.

The third chapter finally issues in the exposition of action-organising principles as ways of dealing with responsibilities delegated to specific groups for the sake of organisation of action. These groups are either scientific disciplines or professions. Professions and disciplines, it is argued, are the legitimate representatives of the domains of nature and of politics. I thereby try for a socialised version of classical epistemology, one in which scientific objects and political subjects are not represented mainly by some idea or some concept (the signifier), but rather by disciplines or professional groups. The main rationale behind this move is to get to scientific disciplines and professional groups in ways that are primarily social and practical, not theoretical. We have to listen to what professionals say about their domains of expertise, but we also have to take a look at what they do and which consequences their actions come to have. These two aspects do not always converge. Insofar as policy formation frequently takes experts' testimonies as their basis, this is a significant intellectual and practical problem.

I then start to approach the main site of the project, which is constituted by the triangular relation between laboratory, clinic and life-worlds. I give a brief overview of the modernisation of medicine as centred on the instigation of experimentally established knowledge as the main basis of rational action. This is done through reference to Claude Bernard's ethos of research and by an exposition of the therapeutic revolution in medicine that took place within immunology and bacteriology at the turn of the 19th and 20th centuries.

In chapter five I turn to the description of some central moments in the creation of the gene as a principle for understanding heritage and physiological development. One significant part deals with the transition from a biochemical understanding of genetic mechanisms to an understanding of genetics as exchange of *information* as articulated in Francis Crick's Central Dogma. The destiny of the dogma is then followed through the revolution in DNA technology, in which the industrial and commercial potential of molecular biology started to materialise, before I turn to the developments in sequencing and mapping technology that finally issued in the Human Genome Project. The historical description follows the

interpretive framework insofar as it starts with the experimental conception of the gene, then follows the transfer of the gene and its organising principle(s) into society. This also means that most of the project is concerned with developments in the USA, as that has been the country in which the main developments have taken place.

The question is asked whether the central dogma (as understood through the new platform of genomics) as well as the technological objects issuing from it, can serve to organise a reorganisation of health care on a broad basis. So far genetics has been restricted to a limited scope of disorders (the Mendelian), but the ambitions of genomic medicine is to establish the genome at the centre of the understanding of most common diseases.

I then (in chapters 8, 9 and 10) turn towards regulatory issues. Two problems are raised concerning the introduction of intellectual property rights into the life sciences: what happens to regulatory measures as the object to be regulated, the gene, is turned into an immaterial object of the information economy? And what can be said about the consequences of the strong commercial influence for the development of genomic medicine?

Finally, in the chapter on autonomy, I try to gather the issues of the previous chapters and to see them in the light of emerging roles for the patient. It is argued that developments within genomics as well as bioethics work together in constructing the patient as a rational decision-maker, and that these developments may lead to a transfer of risk responsibility from the health care system and to the single patient.

Before starting I would like to emphasise that I do not believe to have succeeded with all the above ambitions. I do, however hope and believe that some of the perspectives developed may be sustainable, and that they may pose questions worth of future investigation. Aristotle said that philosophy is a venture into the unknown. I have tried to follow his dictum and to go beyond my own field. One important goal of such a move is to try to engage in a constructive dialogue with other disciplines about issues of a general concern. It should, however, be kept in mind that this is a work in philosophy, not in history or in sociology, and that the arguments should be judged accordingly.

1. Appropriating Heidegger

The situation always prevails. In what the senses of
sight, hearing, and touch convey, in the sensations of
color, sound, roughness, hardness, things move us
bodily, in the literal meaning of the word

Martin Heidegger, *The Origin of the Work of Art*

Martin Heidegger, a follower of Nietzsche, took his philosophy to constitute a radical break with the western tradition of thought, as practiced from Socrates and onwards. I would like to stress that this break was not, and could not be, total. From a hermeneutic point of view, this would be something of an impossibility. In many ways then, his thinking constitutes a continuation of the thinking of Aristotle, and parallels may also be drawn towards Spinoza and towards Romanticism.

Anyway, if we take Descartes as the main figure of comparison, we will be on safe ground; Heidegger does indeed break radically with cartesianism. Not infrequently then, hermeneutic thinkers use the critique of cartesianism as an important momentum in the development of their own position (Rorty 1979; Bernstein 1983; Dreyfus and Dreyfus 1986; Taylor 1989). For the present purpose, this critique is especially significant from two points of view: 1) the understanding of the body, and 2) the understanding of knowledge. The two are not to be separated other than for analytical purposes, and they both find their main articulation within the framework of Being-in-the-World.

Two anthropologies

The main target of critique, we may state, is the image of the disinterested observer; the subject that stands over against the world in order to contemplate it through its objective properties. The *subject*, a construction of Descartes', was not intended in the sense of *subjective*, as most commonly used today. On the contrary, the Cartesian subject could be established only as co-relative to objective reality. In the scholastic tradition, stemming from Aristotle, the *subjectum* was not represented as the person doing the thinking, but rather as that which was thought upon; the subject of the investigation.

The Cartesian subject received its status through the re-establishment of the method through which truth was to be arrived upon. I will not consider the scholastic method in any depth, but

contend myself to quoting Aristotle on scientific methodology as diverse and context-dependent: "Since there are many actions, arts and sciences, it follows that their ends are many too – the end of medical science is health; of military science, victory; of economic science wealth" (Aristotle 1955:63). Hence, the methodology depends on the end of the science, the craft or the action, as well as on the subject matter of investigation: "…it is a mark of the trained mind never to expect more precision in the treatment of any subject than the nature of that subject permits…" (*ibid*, 65).

Descartes diverged radically from Aristotle. His universal method was closely connected to the new natural sciences and as such founded upon the ideal of mathematical geometry. Not only was Descartes the founder of modern philosophy, he is also regarded as having founded analytical geometry, and he applied the method thereby developed also to other sciences. Mathematics, then, was the foundation of the Cartesian subject:

"Until Descartes, every thing at hand for itself was a 'subject'; but now the 'I' becomes the special subject, that with regard to which all the remaining things first determine themselves as such. Because – mathematically – they first receive their thingness only through the founding relation to the highest principle and its 'subject' (I), they are essentially such as stand as something else in relation to the 'subject', which lie over against it as *objectum*. The things themselves become 'objects'" (Heidegger 1978:303).

The notion of the subject is dependent upon the notion of mathematical certainty. From signifying the 'subject-matter' at hand in the concrete case (Aristotle), now the subject-matter is in each and every case treated to and subsumed under the same methodology, namely that of mathematics, thereby to be represented to the subject in all its clarity and distinctness. In the introduction to the *Discourse de la Méthode*, Étienne Gilson writes that

"Une fois accoutumé aux exigences de la vraie méthode, l'esprit pourra les transporter dans d'autres domains que les mathémathiques, et concevoir par consequent la possibilité d'une *mathématique universelle*. Entreprise chimérique au premier aspect, parce qu'il semble impossible de tout réduire au calcul et de metre les problèmes de la métaphysique ou de la morale en equation. De fait, il ne sera même pas possible de réduire au calcul les problèmes de la biologie, de la chemie, et parfois de la physique; il restera cependant possible de les traiter mathématiquement" (Gilson 1946:11).

How was it possible, Gilson asks, to reduce the objects in their many-sidedness to the clear and distinct ideas of mathematics? This was accomplished through a new ontology ascribing primacy to those properties of the objects that offered themselves to mathematical analysis

through objective operations of measurement, whereas those depending on the senses were relegated to a secondary position.

These objective properties were what Descartes, following Galilei, termed *primary qualities*. By taking such a stand towards the world, the observer is capable of abstracting from any personal interest or aesthetic preferences that he may take in the world. Thus, by doing away with these *secondary qualities*, truth may be grasped in all its clarity and distinctness. The primary qualities were those properties of the physical and mechanical universe that could be analysed by way of quantification: length, breadth and depth, whereas secondary qualities would be those of smell, colour, tastes and the like. By this sharp division, the world is split into two dimensions; one is objective and external, the other is subjective and internal. Causally, the primary qualities relate to the internal as stimulus to respons. When I see something as red, or when I taste something as sweet, this is nothing but confused impressions of the objects that caused my feelings. Hence, the qualities of redness and sweetness do not exist as such, in an external entity, for instance an apple. They are nothing but "…the various dispositions of these objects [primary qualities] which have the power of moving our nerves in various ways" (Descartes 2003:book CXCVIII), thereby causing the inner representations/sensations of redness or sweetness. Hence, subjective feelings distort our understanding of objective reality. We therefore have to rid ourselves of the secondary qualities in order to arrive at the clear and distinct ideas of the primary qualities.

If we turn to modern medical nomenclature, the division between primary and secondary qualities is most clearly expressed as the division between objective *signs* and subjective *symptoms*. The idea is that the symptoms, as experienced by the patient, are subjective expressions of the underlying objective causes, the *signs*[3].

What then, is the primary interest within the Cartesian attitude of dis-interestedness towards the world and the body? The answer is a strange one insofar as the purpose of dis-interested knowledge is that of gaining prediction and control, which undeniably must be linked to some interest[4].

[3] As will be argued at a later stage: In genetics, the relationship between primary and secondary qualities resembles the relationship between *genotype* and *phenotype*.

[4] One modern way of rationalising this seeming contradiction away, is to do as Rudolf Carnap, and relegate questions of interest to the domain external to science itself, to the pragmatic. In the analysis of Max Weber,

On the one hand, we have the relationship of the mind to the body: "This I (that is to say, my soul by which I am what I am) is entirely and absolutely distinct from my body, and can exist without it" (Descartes 2001:6). On the other hand, this attitude is closely *linked* to man's being-in-the-world. Through knowledge, man frees himself from the causal bonds that tie him to the world, and he gains control over himself and his environment: "To be free from the illusion which mingles mind with matter is to have an understanding of the latter which facilitates its control. Similarly, to free oneself from passions and obey reason is to get the passions under instrumental direction" (Taylor 1989:149).

The reason behind this seemingly self-contradictory view lies in a pre-existing ontology in which the body and the world are perceived in terms of *mechanics*. What we have here is one of the first articulate moves towards what Max Weber, at a much later stage, was to diagnose 'the dis-enchantment of the world': the emptying of the world's naturally given meaning through its rationalisation.

The universe is no longer seen as displaying a natural order, as found in the ancients, but is rather depicted as dead matter moved forward by mechanical necessity. In the universe of Aristotle or Plato, every thing and every organism tends towards its natural place within a larger whole. The organism, and not just the mind, is thus understood as having its own moving force within itself, rather than outside itself, and thus as moved by its own nature towards its proper place within the environment at large (Heidegger 1967). In the case of Aristotelian ethics, man is moved by an understanding of the Good already rooted in his socio-biological nature (not to be confused with modern socio-biology). Movement and understanding are therefore depicted in a circular, rather than a linear, manner: as tending towards its own completion and as seeking this on the basis of a prior understanding of its own goal. Thus, the moving cause, strange as it may sound, actually and factually comes into being *after* the movement caused, but only because there existed some prior understanding as to its desirability and reality[5].

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mirroring Nietzsche, this state of affairs is responsible for the modern value nihilism: Rationality is objective, whereas value is subjective.

[5] For some modern, Aristotelian descriptions of the circularity of the understanding and the explanation of social action, see for instance (Collingwood 1956; Winch 1958; Skjervheim 1959; von Wright, 1971; Taylor 1971-1972).

In Descartes, there is no longer such a proper place for man and there is no prior understanding of the Good whatsoever: Man is inserted into a physical and mechanical universe seemingly without pre-established order. The implications are, as mentioned, radical:

"…this involves more than just the rejection of the traditional ontology; it also does violence to our ordinary, embodied way of experiencing. We have to disengage ourselves from this, for Descartes, irremediably confused and obscure way of grasping things. To bring this whole domain of sensations and sensible properties to clarity means to grasp it as an external observer would, tracing the causal connection between states of the world or my body, described in primary properties, and the 'ideas' they occasion in my mind. Clarity and distinctiveness require that we step outside ourselves and take a disengaged perspective" (Taylor 1989:146).

The body is regarded as a closed-off mechanism rather than as an organism capable of establishing its own qualitative distinctions in interplay with the environmental order. Thus, the body was depraved of its inherent normative significance as well as its contextual dependence. Similar conceptions are highly operational in the genomic era, where physiological function is conceived as a "molecular machinery". Take for instance the following quote from the Nobel laureate Jacques Monod, describing the cell as a biochemical system:

"The entire system is totally, intensely, conservative, locked into itself, utterly impervious to any 'hints' from the outside world. By its properties, by the microscopic clockwork function that establishes between DNA and protein, as between organism and medium, an entirely one-way relationship, this system obviously defies 'dialectical' description. It is not Hegelian at all, but thoroughly Cartesian: the cell is indeed a machine" (Monod 1971).

It would be too easy to state that Heidegger turns the Cartesian analysis upside down. Rather: he entirely rejects its language. Still, we will not miss his point if we, as a preliminary, state that he does indeed inverse the logical order of investigation. The world, in which we, as bodily beings, find ourselves, is the place to start: "Ontologically, 'world' is not a way of characterizing those entities which Dasein essentially is *not*; it is rather characteristic of Dasein itself". It possesses a "pre-ontological existentiell signification" (Heidegger 1962:93). Centrally, this means that there will be no place to turn in order to rid ourselves of some interest we may take in the world, and that Descartes' secondary qualities cannot be excluded by some primary reflexive move. In the last resort, Descartes' disinterested observer does not exist, and there is no last ground for cognition, no being outside this world. It is this state of affairs that is expressed by the existentials of *facticity* and *thrownness* (*ibid*.): man always finds himself as thrown into this or that situation, and he cannot step outside of his factical

existence within a certain context. This is furthermore one in which he generally takes a particular interest. Therefore, also the position of the Cartesian observer must be understood as engaged in some project in which he takes an interest in the world: "…a state-of-mind implies a disclosive submission to the world, out of which we can encounter something that matters to us" (*ibid*., 138).

This then, is the significance of Being-in-the-world as the primary phenomenon of hermeneutic analysis: we have to start with the relationship *between* man and world as it shows itself directly. We cannot, as did Descartes, abstain from the world in order to know it and ourselves. Rather, to give a description of the world as a phenomenon means to "…see what shows itself in 'entities' within the world" (*ibid*., 91). That which appears through this description of entities is not to be regarded as something fundamentally other than ourselves: "Looking at something, understanding and conceiving it, choosing, access to it – all these ways of behaving are constitutive for our inquiry, and therefore are modes of Being for those particular entities which we, the inquirers, are ourselves" (*ibid*., 26-27).

Heidegger's analysis opens up a way of asking about objects in the world that does not cover up their value-ladenness. The objects around which we organise our activities are 'invested with value'. I will use the term "epistemic things" or "epistemic objects" for those objects that are established through knowledge-based practises of analysis or production (Rheinberger 1997). According to traditional modes of analysis, such a conceptual construction may seem an oxymoron, with "episteme" normally belonging to method or procedure, and with "thing" as referring to the material aspect or even as making an ontological claim. From the perspective of being-in-the-world, however, there cannot be any such fundamental difference. Practices are "determined" by methodological considerations, by the "being" or the materiality of the object, as well as social conditions. As clearly as these different aspects cannot be reduced to one of the others, as clear is it that they cannot be regarded in absolute separation from each other. I will argue that the way to keep them all within a holistic view, goes by way of analysing both epistemological and ontological claims from the point of view of (social) *action.* This also entails that we will have to step out of the Heideggarian framework.

The social organisation of objects, epistemic or otherwise, says something important about dominant values of the practice in question. These need not coincide with the dominant

legitimisations of the practice, but are rather to be regarded as functions of the 'total' environment of the object, of the interests and the resources necessary for the manufacture of the object. Values are, *per se,* embedded in the efforts to create epistemic objects. As such, they are both tacit and articulated (Polanyi 1967; Johannessen 1990). For instance, it need not surprise that the social 'Being' of the gene has been and still continues to be, a nexus of differing definitions and understandings (Fox Keller 1995). Although referring to the same scientific findings as the fundamental outcome of their activities, the validity claims of the pharmaceutical industry or biotech companies may be sharply at odds with those of publicly funded research (Krimsky 2003).

In order to get at this problem complex, we need access to the gene or the antibody in ways that are primarily social, and not epistemological. Although this in many cases means that we do not go into great detail as concerns the epistemic characteristics of the gene, it does not mean that it is 'black-boxed'. The central claim is that also epistemic objects are primordially social 'Beings' (Ziman 2000) because they have real social consequences.

Insofar as we do not ask about the 'Being' of science or technology, as does Heidegger, we have to restrict ourselves to actions through which they are constituted and the actions that are made possible through objects of science and technology. Meanings are embedded in practices; they are what grant them coherence and intelligibility (or the lack of such). Hence, we may transcribe Heidegger directly: From stating that

"..the *Being* of entities 'is' not itself an entity", but rather "that which determines entities as entities", to

"The interactions with entities are themselves not entities, but that which determines entities as entities".

Epistemic entities possess their status only to the degree that it has been given to them through negotiations with material reality organised within the social sphere (hence the primacy of 'historical epistemology'). Indeed: the social character of the epistemic object penetrates right into the sphere of the laboratory or the computer.

Heidegger's procedure

Even though Heidegger's initial question is heavily metaphysical, it is designed so as to direct us towards the primacy of worldly affairs. Hence the centrality of the conception *being-in-the-world*: "Ontologically, 'world' is not a way of characterizing those entities which Dasein essentially is *not*; it is rather characteristic of Dasein itself". It possesses a "pre-ontological existentiell signification" (Heidegger 1962:92). In a sense, we already know the answer to the question, and the question is given its shape and content on the basis of this prior understanding. The way to approach the problem, then, is not by abstaining from worldly interests, as did Descartes, but rather to immerse the analysis in the everyday world of human activity; to "see what shows itself in 'entities' within the world" (*ibid*.).

The Cartesian notion of disinterestedness has no place within such a framework. The structure of *caring (Sorge*) for oneself through one's (close) environment is the basis of any understanding of the world whatsoever: "The kind of dealing which is closest to us is, as we have shown, not a bare perceptual cognition, but rather that kind of concern which manipulates things and puts them to use…" (*ibid*., 95). In the second part of *Being and Time,* the structure of care is unfolded as constitutive of the structure of anthropological time. Exactly because there is no privileged starting-point for the investigation of being, we always find ourselves as (f)actually existing within this or that 'state-of-mind' (*Befindlichkeit)*. The English translation 'state-of-mind' is inferior to the German expression, insofar as it does not express the fundamental relatedness towards the world: we always find ourselves in situations in which something is at stake, namely our present and continued being-in-the-world. "It is essential to the basic constitution of Dasein that there is *constantly something still to be settled [eine ständige Unabgeschlossenheit]*. Such a lack of totality signifies that there is something still outstanding in one's potentiality-for-Being" (*ibid*., 279). Human existence then, is fundamentally temporal in the sense that it is always (or at least, most of the time) caught up in networks of past, present and future events, some of which are taken to be more fundamental to our well-being than others. We inscribe certain options and courses of events with values and qualities essential to our feeling of self; to our identity and our belonging in the world. Hence, the world possesses certain meaning-structures through which we may improve our being-in-the-world[6].

[6] In passing: only in this manner does the notion of *choice* make sense, as taking place within a network of meaningful events that we inscribe with differing degrees of value or quality.

As already indicated, this structure of the world is constituted by the meaningful inter-connection of useful things. Hence, the investigation starts with our dealings with the entities that are closest to us. Because these are the ones that we invest with the most value, they also serve as the necessary point of entry into the question of being: " In so far as Being constitutes that which is asked about, and 'Being' means the Being of entities, then entities themselves turn out to be what is interrogated" (*ibid*., 25-26). As a common denominator, Heidegger uses the term *equipment*. We relate to the world through the use of equipment by that special mode of care that is called *concern* (*Besorgen*):

"…having to do with something, producing something, attending to something and looking after it, making use of something, giving up something and letting it go, undertaking, accomplishing, evincing, interrogating, considering, discussing, determining" (*ibid*., 83).

The fundamental character of equipment is *not* that which we may get from a theoretical analysis of its properties; mass, weight, length, materiality and so on. We always first learn about equipment through practice. Equipment carries the special characteristic of referring to some further object; it exists within a chain of object-events as something 'in-order-to'; as tools for achieving something else. One example used by Heidegger is the building of a house: I use the hammer *in order to* drive the nail into the board. I drive the nail into the board in order to build a structure of boards that can carry the roof of a house. In this way, each piece of equipment fulfils its purpose only in relation to a further piece of equipment, which again is used for the manipulation of some further object, and so on.

This way of reasoning may also be applied to the more complex case of scientific activity: We mix DNA with nucleotides and polymerase enzyme in a test tube in order to put it on a heater. This we do in order to start a chemical reaction whereby two strands of DNA separate, then copy themselves in exponentially increasing numbers. These clones are in turn used for the effective sequencing of human DNA, which again may be used to detect infections, to make diagnosis, trace the human origins to Africa, to launch venture investments on Wall Street and so on.

What is the final aim of these chains of object-events? For now, let us stick to the more simple case of the house. One answer would be: the house itself is the final purpose. This is expressed by the term 'towards-which' (*das Wozu*). When manufacturing relatively simple

entities, the goal of the process will be immanent to the single operations of the building process itself. But this would be a partial answer only, because it still somehow covers up the fundamental interest that is at the basis of the undertaking. In the end, this whole chain of events is instigated by me in order to *care* for that entity which I myself *am*. Hence, the house itself is not the final goal of the operation; it is me, and, in addition, whoever I plan to lodge inside it. Although the boards of the house may be measured, weighted and shaped according to strictly quantitative measures, the fact still remains that they are invested with value and interest, which in the last resort point back to me as the one doing the investing. Hence, the house is an important constituent of my being-in-the-world. Generally: houses are important constituents of *our* being-in-the-world, as fundamental meaning-structures of our inhabiting and feeling at home in the world. Whether one has a house in which to live or whether one lives on the street; these possible states of affairs usually make quite a difference for one's state of mind (*Befindlichkeit*).

The point of being-in-the-world is to situate the analysis in this world and not in some parallel or transcendent universe. Hence, even if the final goal of the undertaking is the understanding of Being itself, Heidegger starts out within our everyday environment: "In the disclosure and explication of Being, entities are in every case our preliminary and our accompanying theme…; but our real theme is Being". The notion "in every case" should be remarked upon: Even though we proceed towards greater levels of generality, we also remain with the things that we already know. In the words of Kant: every concept should have as its counterpart a possible experience. The alternative is idealistic dogmatism, which is precisely the thing to be avoided. In short, Heidegger starts out with the thing-hood of the world, and he depicts it as chains or networks of meaningful action-events. Because these networks are not indifferent to us, but rather constitutive of the entities that we ourselves are, we always find ourselves (factically) as being in this or that state-of-mind (*Befindlichkeit*) or mood with regard to our further existence in the world. We *project* our future on the basis of the past and present.

This understanding forms the basis for the understanding of anthropological time in part two of *Being and Time*: the action-events project the horizon from which past, present and future events receive their significance. From this derives the potentialities for authentic or inauthentic existence, and as such, there is constantly something at stake in our being-in-the-world. Without pertaining to follow Heidegger all the way: from the understanding of the potentiality of authentic existence as grounded in the phenomenon of temporality, something

like an answer to the question of the meaning of Being is sought out.

Next, I will raise the following question: Heidegger's procedure is here situated within the context of building a house. But what if this was not our starting point, but rather the procedure of analysing DNA in a laboratory, as also described? I will try and argue that a context of increased complexity will require of us that we make the step from hermeneutics simple to what I, taking inspiration from Ulrich Beck, name "reflexive hermeneutics".

Towards sociology…

Heidegger is often charged with being a too abstract, too deep and too metaphysically oriented thinker. For instance, at the same time as Habermas *praises* him for breaking with the solipsism of Descartes, Kant and Husserl, he *criticises* him for not completing the movement towards inter-subjectivity and for being too obsessed with essences and totalities.

Indeed, this criticism has something going for it: Heideggerian analyses typically concern themselves with questions about the meaning of Being, the essence of truth, technology, modern physics or art. In one sentence: because he does not step down from the same metaphysical ivory tower that he so strongly has contributed to tearing down, his thinking ends in a peculiar position when it comes to questions traditionally belonging to what is termed *practical* philosophy.

Intersubjectivity may be defined as 'man's relation towards himself as intermediated through his fellow beings and the common world in which he finds himself along with others'[7]. This definition should mean that a good working conception of intersubjectivity should also take the perspective of 'the other' into account so as to be flexible, dynamic and properly dialogical. Obviously, central elements in Heidegger's writings fall short of such a demand; he prefers to stay within metaphysics in the classical sense of the word, a position which renders him a somewhat archaic presence in modern philosophy.

Still, as pointed out by David Kolb, Habermas is mistaken if he takes this to be a decisive blow to the Heideggerian undertaking (Kolb 1992). In criticising Heideggers metaphysical leanings, Habermas himself relies upon a conception of intersubjectivity that is itself

[7] This is an extended version of the treatment of intersubjectivity as given by (Skjervheim 1959).

questionable, and which has been thoroughly criticised, for instance by (Wellmer 1986)[8]. Because he is in a sense himself positioned in his own ivory tower, Habermas himself miss out on the potentialities for a properly working conception of intersubjectivity already present in Heidegger's philosophy[9]. Hence, in criticising Heidegger's obsession with totalities and essences, he himself remains situated within the point of view of an abstract and questionable 'totality', that of the ideal situation of speech.

Anyway: Kolb does not see this conflict of philosophies as decisive. Rather, he suggests that we recognise the obvious differences between the two projects, and that Heidegger's approach may be retained while at the same time paying attention to the valuable parts of Habermas' critique.

Habermas regards intersubjectivity as a constant learning process arising in the life-worlds, and as intermediated through propositional claims to truth and validity in a community of investigators. The meaningful experience of truth (*Sinn*) has to be distinguished from truth propositions (*Geltung*). In this lays the opening for a conceptual and communicative ascendance towards truth and validity (Habermas 1981). For Heidegger, on the other hand, there can be no such dialectics of truth: truth is in a sense always already there. Still, this does not mean that the world is a static one, or that it does not in a sense depend upon regional interpretations. Also for Heidegger the world is dynamic. But it does not primarily change through culturally inflicted causal processes, i.e. intrusions from the system world or communicative learning; it changes because of its inherent *temporality*:

"To talk about implicit concepts or propositions [as does Habermas] is to stay within the picture of a subject or a community that uses conceptual tools to organize its experience. Heidegger wants to undercut that picture by showing how beings are revealed as meaningful in the happening of lived time. That happening is not the secure appearance of something mobile before a stable self-present subject or community. Temporality is not a structure made available for a subject to use or reflect on; it is an event in which Dasein finds itself already stretched out in a particular coming together and going apart in a skein of presences made possible by absences" (Kolb 1992:688).

[8] A critique that has been recognised in Habermas' later writings.
[9] Without going further into the problematic here, I suggest that Habermas parts ways with Heidegger already in his conception of life-worldy action. In many ways, Heidegger's conception of the life-world remains richer than that of Habermas, as Habermas comes to rely upon a conception of action taken from speech action philosophy. In that way, his understanding of life-wordly action remains closer to conceptions of rational choice than that of Heidegger or, for that matter, Wittgenstein.

Heidegger's world, on the other hand, consists in "the matrix of meaningful relations among things in the world that reveals those things" (*ibid.*). I will return to this point in some length. First, however, I will follow Kolb's resolution of the question of intersubjectivity in Habermas and Heidegger. The decisive point, he says, is that the world as portrayed by Heidegger does not possess 'totality' in the sense attributed to it by Habermas. This is so both in the unfinished part of *Being and Time* and in Heidegger's later writings, where temporality is given primordiality over Being. Hence, Derrida's conception of *différance* represents a logical continuation of Heidegger's analysis of temporality (Derrida 1976).

I will remain with the Heideggarian analysis of things/objects. But I will try and give them a somewhat more practical interpretation than does Heidegger himself, one which is more inspired by contemporary philosophy of science (for instance, Ian Hacking and Steve Fuller) and sociology (Beck). The point is this: in studying epistemic objects as social entities, it will not do to operate with strictly separated ontological domains: law, biology, medicine, industry, politics and so on.

One reason for this is that the apparent exclusiveness of the object domains of these different regions are not as exclusive as may seem at outset. Only if we remain within a theoretical attitude towards epistemic objects do we fail to grasp this point, that is, if we continue to consider them in terms of theory, be that as pure "information" (Crick 1958), their 'essence' (Heidegger), or if we continue to aim for some final synthesis at the end of an infinite process of learning, even though it remains a regulative ideal (Habermas). Considered from the point of view of practical interaction, the questions arising from the integration of new technologies into society need to be posed in terms of the social being and meaning of epistemic objects (Ziman 2000). This point must be maintained as primordial in relation to questions concerning epistemic truth. Of course, this perspective is not foreign to Heideggerian thinking. But because he remains within his 'metaphysical attitude', he fails to regard the social destiny of technological and scientific objects: what happens to epistemic objects when they transgress the boundaries of the world in which they are created and in which they find their primordial validity *qua* epistemic objects? A passage from Georges Canguilhem, remarking upon the *difference* between the experimental context and the normal environment of living beings, makes for a good illustration:

"If we may define the normal state of a living being in terms of a normal relationship of adjustment to environments, we must not forget that the laboratory itself constitutes *a new environment* in which life certainly establishes norms whose extrapolation does not work without risk when removed from the conditions to which these norms relate. For the animal and for man the laboratory environment is one possible environment among other. Certainly, the scientist is right in seeing in his apparatus only the theories which it materializes, to see in the products used only the reactions they allow; he is right in postulating the universal validity of these theories and reactions, but for the living being apparatuses and products are the objects among which he moves as in an unusual world. It is not possible that the ways of life in the laboratory fail to retain any specificity in their relationship to the place and moment of the experiment" (Canguilhem 1991:148-149).

Seemingly paradoxical: the conditions under which the epistemic object gains its universality is simultaneously the conditions that *limit* its validity. And, one further step removed from the experimental context: the initial conditions of the experiment; be they theoretical, instrumental, technological or economical, are themselves conditioned by social interests and validations, that may eventually be influenced by scientific developments resulting from experimental activities. Experimental activity, then, reside within complex fields or networks of feedback mechanisms. Insofar as we continue to consider scientific activity in terms of epistemic value only, or in terms of its metaphysical significance, these complex relations are covered up.

A related, but somehow more philosophical reason why we have to readjust Heidegger goes as follows: it has already been mentioned that Heidegger's writings underwent changes from the early to the late period. Whereas in *Being and Time* the phenomenon of Being-in-the-world is constitutive for anthropological time, the order is so to speak reversed in his later writings, where temporality in a sense is prior to Being. Hence the critiques of such diverse thinkers as Habermas and Derrida. These critiques also indicate that Heidegger underestimated the value of language in his earlier writings. Time and language so to speak 'uproot' the unitary phenomenon of Being.

This may also be restated as follows: unless we want to remain within the essentialist and metaphysical position of Heidegger, it will no longer do to try and think time and place as unitary phenomena. In modernity, the two have become separated by globalising processes of standardisation, one early and significant event being the global distribution of mathematised time through the mechanical clock (Giddens 1990).

For purposes of analyses of concrete societal processes then, we have to recognise the need for differentiation, and this must be situated within concrete socio-historical development:

from traditional society, possessing a relative unity of time and place, through the dis-embedding of Being in modernity, up until the late modern condition, where a certain *tension* exists between standardising processes in globalised time and the need for localising, embedded and re-embedding processes in concrete space:

> ”The dynamism of modernity derives from the *separation of time and space* and their recombination in forms which permit the precise time-space ‘zoning’ of social life; the *disembedding* of social systems (a phenomenon which connects closely with the factors involved in time-space separation); and the *reflexive ordering and reordering* of social relations in the light of continual inputs of knowledge affecting the actions of individuals and groups” (Giddens 1990:16-17).

The tension may be formalised as follows: globalised and standardised time find their conceptual counterpart in the geometrical conception of empty space. But this is not the conception of space normally found within local communities and practices; these are by necessity situated in concrete *places*, and so they will also display substantial degrees of concrete time, in Heideggers terms, anthropological time.

As will be seen, this tension between standardising knowledge situated in abstract time and space and the need for locally situated knowledge is the medium, or the stratum, in which reflexive modernisation takes place. The ambiguity of Being that is entailed therein is valued differently by different authors. For instance (Habermas1981) is critical of the ‘colonisation of the life-world’ by the system world. Still, it seems that he operates with a rather rigid distinction between them, and that this rigidity stems from a too linear view of the development of the system world(s) (Beck 1993). On the other hand, we find authors like Brian Wynne, emphasising the life-world as the only “real” dimension and downplaying the epistemic claims of expert systems as social constructs (Wynne 1996).

Hence, the question cannot be one of either-or, standardisation or localisation; reflexive modernity is the time of the *–and* (*ibid.*). The interesting questions, then, centre on *how* best to deal with the tensions of late modernity, not of taking extreme positions. Admittedly, die-hard proponents of the Human Genome Project do exactly that, insofar as they view integration of standardising processes of knowledge into the life-worlds as unquestionably beneficiary and as a rather one-dimensional process: efficient social action is regarded almost exclusively along the lines of scientific progress and utility. On the other extreme we may position a reactionary reading of Heidegger: as one refusing to make the step into modernity, preferring to deal with rather simplistic and archaic models of social action (chopping wood,

going to the market and so on), thereby retaining the unity of time and being, temporality and space. In the words of Ulrich Beck, this anti-thesis to the simple modernistic view, is characteristic of processes of *Gegen-modernisierung* (Beck 2002).

The initial problem was this: the categories of the Heideggerian analysis are too loaded with metaphysical content. Insofar as metaphysics are desired, they must be 'social metaphysics', hence practices, and not metaphysics proper: "Writ large, metaphysical practice results in the schemes that societies design for classifying their members" (Fuller 1988:32)[10]. Law and medicine are prime examples of such practices, a different name for which would be 'regional ontologies'. The integration of such ontologies into society at large will be dealt with in some more detail bellow; clearly *any* ontology will not do. As a preliminary: regional ontologies arise within relatively closed of systems of action that are centred around the methodological, technological and instrumental creation and reproduction of epistemic objects, or around categories of thought and action specific to that particular region (for instance the legal system). Both to the actors within the action systems and actors in their wider environment, these ontologies will, to a certain extent, take on naturalised and self-evident meanings. In order to achieve this, they require

> "…a restructuring of the physical environment and the addition of new technologies, all designed to make the signs of membership in the relevant classes more evident to the trained eye. This fact should come as no surprise, and indeed, it explains why a metaphysics worthy of the name must be social: namely, if a metaphysics is to appear as an account of 'how things really are', then its categorical distinctions should seem 'natural' even to the perception of someone who is unlikely to understand or accept the theoretical justification for that metaphysics" (*ibid,* 33).

Now, given this wide, social interpretation, the following should be clear about regional ontologies: 1) the epistemic truth of objects, although a necessary component in their manufacturing, cannot do justice to their wider social function. For this purpose, we will do better to look for some of their basic social functions, in other words, the *interests* they are expected to redeem; 2) as already mentioned above, modernity is grounded upon a set of professionalized practices that do not merely deal with their own closed-off regions. Moreover, the different regions, for instance law, medicine, politics and industry, may also, in specific times and places in history, be said to support each other mutually, or to question each other's claims to ontological validity. For instance, the establishment of medicine as a

[10] Although no Foucauldian himself, Fuller's conception builds upon Foucault's idea of law as social metaphysics.

profession was only possible under conditions of the rule of law, which again presupposed a certain political climate supportive of medicine's organisation into one coherent system (Porter 1997). Through the strengthening of medicine, the politics of the nation state were propelled forward; 3) from this, it seems to result that what has been naturalised may also be 'de-naturalised', and that social ontologies may indeed be questioned. According to Beck, such 'de-naturalisation' of social ontologies may be regarded as intrinsic to the individualisation processes of reflexive modernity (Beck and Bonss 2001).

Meanings of modernity

Returning to Heidegger we may distinguish between five different layers of generality: 1) individual propositions, 2) reflective constructs (some theory, for instance that of the gene), 3) regional understandings/ontologies of different kinds of beings (art, law, medicine…), 4) the overall understanding of being that gives unity to an epoch, in modernity termed *das Gestell*, and, finally 5), the formal conditions of the understanding of being whatsoever (Kolb 1992)

Although insisting that the problem was always the same, Heidegger dealt with category number five in different ways throughout his life (Mitcham 1994). As already mentioned, this level will be left out here. The question remains, then, of how to deal with the remaining four.

One major contention of Habermas is that Heideggers obsession with totalities renders the critique of regional, theoretical or epochal understandings a futile task. As articulated by Kolb:

"…there remains in Heidegger a one-way dependence of propositions on the prior revelation which makes them possible. As something like a transcendental condition, that revelation is not to be interfered with by any ontic activity…Understandings of being are not 'transcendental' in the precise subjectivist sense in which Heidegger employs the word, but they fit the more general sense derived from the neo-Kantians; they are conditions of the possibility, rather than conditions of the actuality, of individual propositions. They are distinct from and prior to both the logical analysis of presuppositions and the conditions studied by natural or social science" (Kolb 1992:691).

Here the solipsism of Heidegger announces itself: there is a kind of philosophical understanding, prior to any scientific or lay understanding, sufficient to determine the overall being of an epoch or regional ontology, and this understanding goes altogether untouched by any individual proposition or validity claim: "Heidegger inserts a level more pervasive than

any philosophical school or scientific theory, but still determinate vis à vis other epochs in the history of being, *and* this determinate level functions as the condition of the possibility of individual propositions" (*ibid*). As an example, Kolb cites Heidegger's reading of the Aristotelian theory of motion: in the hands of Heidegger, the theory is presented as a direct consequence of, indeed determined by, the more general Greek conception of the physical universe. But this cannot be, says Kolb. Even in his own time, Aristotle's theory of motion was in dispute, and some of its major flaws were pointed out. And so there must have been a greater room for disagreement within the Greek understanding of the *physis,* and the 'unity' of the epoch will have to be somewhat more loosely defined.

Heidegger cannot have it both ways: overall transcendental conditions *and* epochal unity containing sufficient specificity for a critical diagnosis of the epoch at the same time. There cannot be a simple, one-way relationship between the different layers of generality referred to above. Although recognising the necessity of different levels of generality and meaning, the interesting thing will not be their 'essences', considered as such and in isolation, but the interplay between them. This point resembles a previous argument: regional ontologies also depend upon each other. In that sense they are not closed off systems. Again, I suggest that the problem can be avoided if we remain with the social being of epistemic objects and action-organising principles rather than isolate ourselves within metaphysics. Importantly, metaphysics must be regarded as intrinsic to some organised pattern of action, as co-relative with the practices in which they inhere.

Recall how the dynamics of the Heideggarian world depends not upon culturally and communicatively inflicted processes (Habermas), but rather upon that of temporality. To a greater degree then, development is something that 'happens', and not something that is instigated by human agency only. The primary characteristic of the modern age is that of the *technological* attitude towards the world, *Gestell* (Heidegger 1978b).

Technology

Gestell means something like a 'framework', or a 'skeleton'. In accordance with the general structure of being-in-the-world, it is at the same time characteristic of specific properties of the world and a specific attitude of man towards the world. It is that particular attitude towards those properties of the natural world that allows for the world to become a resource for exploitation. Through this attitude nature's resources are capable of being stored up and

kept as a 'standing-reserve' (*Bestand*). Man is 'challenged forth' by nature to 'set upon' its resources, to extract nature's energies in such a manner as to be able to store them up, later to be used for some practical purpose:

"Such challenging happens in that the energy concealed in nature is unlocked, what is unlocked is transformed, what is transformed is stored up, what is stored up is in turn distributed, and what is distributed is switched about ever anew. Unlocking, transforming, storing, distributing, and switching about are ways of revealing" (*ibid,* 322).

Through the unlocking of nature's stored up resources, the power concealed in nature, the standing-reserve, is *revealed.* Unleashing the energies of a power plant in order to provide a city with light; starting up a jet plane and taking off; observing the effects of antibiotics distributed in an area struck by an epidemic. In all these cases the standing-reserve, that which has been stored up through the framework of the *Gestell* ('enframed'), is revealed and the technological unfolds. The central importance of technology resides in its potentiality to re-enter the world of practical affairs through action and agency: material agency that has been stored up can be released at will so as to merge with human agency and enhance its powers and its capabilities.

This is a conception of technology that distinguishes itself from that of the pre-moderns: "…whereas premodern technology cooperated with nature to bring forth artefacts, modern technology imposes on nature, forcing it to yield up materials and energies that are not otherwise to be found" (Mitcham 1994:257).

I do believe this to be a useful conception of technology, and as indicated I intend to use the conception of the *standing-reserve* in characterising modern medical technology. But as pointed out to us by Kolb, we cannot use such a conception for the causally and ontically primary determination of an entire period; this would indeed be 'bad social analysis' (Habermas 1987). On the other hand, it is not certain that the view ascribed to Heidegger by Habermas and Kolb is the one that he actually held:

"*Ge-stell* is…presented as a historical destiny or fate that calls on humanity to act in a particular way. It is not, however, a fate that compels in some crude sense. Elsewhere, having contrasted calculative and meditative thinking, Heidegger suggests that associated with such ways of thinking are two kinds of consent" (Mitcham 1994:257).

Mitcham refers us to the essay *Gelassenheit*, in which Heidegger sketches an alternative to technological determinism. Because *Gestell* primarily is an attitude towards those properties of the world that allows for their exploitation, it is clear that we are to some extent determined by this technologically established relation towards the world. We are challenged (forth) by the world to set upon it in such a way as to extract its hidden powers through the framework of *Gestell*. But this is not to say that the world does not also contain different properties, different possibilities of relating towards it (and thereby also towards ourselves). One alternative is the attitude of *Gelassenheit*, in which we are freed from the technological imperative through releasing the things in the world:

"…we can act otherwise. We can use technical devices, and yet with proper use also keep ourselves so free of them, that we may let go of them any time…But will not saying both yes and no this way to technical devices make our relation to technology ambivalent and insecure? On the contrary! Our relation to technology will become wonderfully simple and relaxed…I would call this comportment toward technology which expresses 'yes' and at the same time 'no', by an old word, *releasment towards things* [*Gelassenheit*] (Heidegger 1977:53-54).

This is not a question of an either-or. Technology cannot simply be rejected; it is too much part of our being-in-the-world. As such, it does not simply exist 'out there', as a physical fact, and in our minds as intellectual representations; it is part of our bodily being, of our whole way of relating to the world:

"The machines and apparatus are no more cases and kinds of enframing than are the man at the switchboard and the engineer in the drafting room. Each of these in its own way indeed belongs as stockpart, available resource, or executor, within enframing; but enframing is never the essence of technology in the sense of a genus. Enframing is a way of revealing that is a destining, namely the way that challenges forth" (Heidegger 1978b:335).

Thus, as a way of comporting ourselves towards the world, technology is a process (a "setting-upon") that is determining in the sense of a self-generating and accelerating process: it threatens to drag us into, so as to be encapsulated by, *Gestell*. Consequences may be alienation and blindness to the consequences of technology, and possibly also releasing the full destructive power of its 'essence', for instance the atomic bomb. As such, technology poses the 'ultimate danger', insofar as it threatens to cover up other essential aspects of our relating to the world: truth, art, questioning, freedom…Paradoxically, this ultimate danger also "harbors in itself what we least expect, the possible rise of the saving power" (*ibid.*, 337). I will not pursue this point much further, but confine myself to noticing that on this account,

living with technology is not a matter of *rational choice* in the sense ordinary attributed to the word.

Living with technology and its consequences *can*, however, be regarded as *learning processes*, although not in the Habermasian sense. More appropriate metaphors than those of the rational choice or discourse, is that of living through grief, the overcoming of pain:

> "The overcoming of technology must be lived through, extended and deepened, the way grief or pain can be lived through to the point that it becomes an observed grief or pain and thus in some mysterious way is set aside or transcended. When we suffer or are in pain, we are simply too close to what we are experiencing; we need distance, some self-knowledge, appreciation of who we really are and of our limitations. But this is acquired not through rejection or repression of the pain; it comes only with time and through naming the source of our pain by asking questions and talking about it…" (Mitcham 1994:54-55).

There is a peculiar fact of the matter, then, about using Heidegger's conception of technology for the purpose of social analysis: temporality and dynamism is at the centre of his attention, and so the label of determinism should be ill-suited to describe the movement of his thinking. There is indeed something like alternative ways of being and thinking; every disclosure of one perspective is connected to the covering-up of other aspects of reality. Still, because he remains within his essentialist position, he does not allow for a sufficient plurality of perspectives and alternative voices to come fore.

The possibilities for the opening up of technology, Heidegger says, lay hidden in the essence of the being of technology itself, and can be recovered through the practices of art, questioning and *Gelassenheit*. It is not so much that this approach should be regarded as wrong. Still, we should ask, along with Kolb and Habermas: where is *political* modernity? What about the role of law? Are these nothing but footnotes to technological modernity? The institutions of politics and law also have their own *being*, a relative autonomy, and indeed also their own "objects", namely political subjects. These will not readily be subsumed under the ready-to-hand of equipment described above. Furthermore, the view should not be dismissed that these other spheres of action and thinking also have acted as necessary preconditions for the scientific revolution (Shapin 1999). In this respect, it seems that Heidegger, for the purposes of social analysis, by not stepping out of the metaphysical framework, approaches something like determinism. Therefore it may also be argued that he does not really complete the movement from the theoretical attitude into practical philosophy proper. It seems that

Heidegger also closes up the discourse that he initially has *opened up*. (In sum: the relative insecurity of a dialogical approach is necessary.)

A preliminary conclusion should go something like this then: insofar as he takes the technological attitude to be at the basis of modernity, Heidegger's ascribes a too central place to technology in the characterisation. In so doing, he makes the controversial claim that science is the result of the technological attitude (*Gestell*), and not the other way round. Whereas this move may be in order metaphysically speaking, it should be questioned for purposes of social analysis of science and technology.

Science: The projection of nature through the mathematical?

Heidegger uses a well-known quote from Kant's introduction to the *Metaphysische Anfangsgründe der Naturwissenschaft* as a way into characterising modern science. In order to appreciate the full relationship between mathematics and nature, I will quote Kant in some more length than does Heidegger:

"…eine reine Naturlehre über bestimmte Naturdinge (Körperlehre und Seelenlehre) ist nur vermittelst der Mathematik möglich, und, da in jeder Naturlehre nur so viel eigentliche Wissenschaft angetroffen wird, als sich darin Erkenntnins a priori befindet, so wird Naturlehre nur so viel eigentliche Wissenschaft enthalten, als Mathematik in ihr angewandt werden kann" (Kant 1968:Band 9, 15).

This does not mean, says Heidegger, that it is the concrete amount of mathematics, or the fact that we deploy numbers, which is to be taken as the measure of genuine science. Rather, it is a question of the *mathematical projection* that we bring with us into our analysis of things. Within this picture, the numerical analysis that we usually term mathematical is only the special case of the more general mathematical projection. The mathematical projection is based in the fundamental transformation of the experience of nature that started during the scientific revolution. It has at its basis the quite normal and everyday experience of the naturalness of numbers in describing experience: we all in a sense *know* that if we have three bricks of stone at our disposal and we use one, we will be left with only two. If we pick up two more bricks, we will have four, and so on. As such, numbers only explicate what we already know. It is this naturalness that is transformed into something more during the scientific revolution (what Husserl termed the 'mathematisation of nature'). The self-evidential inherent in the practical use of numbers is then identified with *the counter-factual*

representation of all things through axiomatic and certain knowledge; the transformation of experience onto one flat and indubitable plane. In so doing, the experiential basis of thinking is transgressed: "The mathematical is based on…the application of a determination of the thing which is not experientially derived from the thing and yet lies at the base of every determination of the things…" (Heidegger 1967:288). At the base of the mathematical projection lays a fundamental idealisation, and no possible experience. As an example, Heidegger uses Newton's first law of motion: "Every body left to itself moves in a straight line". But how can this be? The fact of the matter is that there can be no such thing as 'a body left to itself'. Moreover, the conception of something moving in a straight line is only possible on condition of this initial idealisation. Hence, the thing and the straight line only exist as such, as idealisations, as projections unto a wholly abstract plane starting from the certainty in numbers found in ordinary experience.

The mathematical projection, then, may be understood as the framework through which the requirement of absolute universality is ascribed to the raw material of experience. Such a description requires a privileged point of view; one that is uncontaminated by the imperfections of ordinary perception. How is this identification of the universal requirements of thinking with the particulars of experience possible?

Only through the prior identification of the experienced with the thought. This is in turn 'accomplished' through the self-evidentiality of the methodological. Husserl criticised this forgetting of the life-world through 'apodictive' evidence, and he tried to carry out a more fundamental synthesis within the realm of the phenomenological (Husserl 1960). But in so doing he tried to replace one method with another, which in its turn relied upon a different set of idealisations, in the last resort that of the transcendental ego (as did Kant). From the point of view of Being-in-the-world, however, no such final synthesis is possible. The cultivation of one methodological aspect inevitably ends up covering up other aspects and so on; the materiality of the object can never be encapsulated or exhausted by method.

In the background of this scientific undertaking, lies some of the ontological presuppositions already pointed out (Cf. the section "Two anthropologies"). Fundamentally, *nature* is conceived of as a uniform structure that can be brought onto concept by the use of method. It is this metaphysical quantum leap that Heidegger terms the mathematical projection.

"If modern physics must resign itself ever increasingly to the fact that its realm of representation [*Gestell*] remains inscrutable and incapable of being visualised, this resignation is not dictated by any committee of researchers. It is challenged forth by the rule of enframing, which demands that nature be orderable as standing-reserve. Hence physics, in its retreat from the kind of representation that turns only to objects, which has been the sole standard until recently, will never be able to renounce this one thing: that nature report itself in some way or other that is identifiable through calculation and that it remain orderable as a system of information. This system is then determined by a causality that has changed once again. Causality now displays neither the character of occasioning that brings forth nor the nature of the *causa efficiens*, let alone that of the *causa formalis*. It seems as though causality is shrinking into a reporting – a reporting challenged forth – of standing-reserves that must be guaranteed either simultaneously or in sequence. To this shrinking would correspond the process of growing resignation that Heisenberg's lecture [*Das Naturbild in Heutigen Physik*, KR] depicts in so impressive a manner" (Heidegger 1978b:327-328).

Heidegger laments the one-dimensionality of modern science. To him, it has been reduced to a calculative reporting. As seen, one way to interpret this statement is that science has been in the service of the technological attitude from the very beginning. As this 'truth' unveils, science is progressively reduced along with technological advance. From this, we may begin to understand the dangers of the technological: the mathematical projection is, by definition, emptied of experiential basis, and so we cannot oversee the implications of the interventions projected through it.

I have given an exposition of technology and science as described by Heidegger. His analyses are informative insofar as they point us towards a *practical* dimension. Still, this dimension is not yet *social*. It remains "practical" only in a highly metaphysical sense. We are given no real conception of science as experimental, and the focus is upon the theoretical foundations rather than the larger environment within which science and technology are created and practiced. I will therefore try to change the perspective somewhat.

I have pointed to the elements that should be retained in the further analysis: first and foremost the centrality of things in the organisation of the world, which again have to be understood from (within) structured action. In this context, the structuration of action and meaning is organised through those specific forms of knowledge called science and technology. From the perspective of societal action, technology may just as well be regarded as applied science, and not the other way around, as argued by Heidegger. This does not mean, however, that Heidegger's view is discarded as such. But in directing our attention to the ways science and technology are organised socially, we cannot but *defer* the questions concerning their "essence". Furthermore, the question of the essence, of the Being of science and technology, was to be replaced by the more modest questions of the many *possibilities for*

action that they may pose. These arise along with the production and organisation of knowledge within different social groups, and cannot as such be readily defined. In the terms of Charles Taylor, they have to be *articulated* (Taylor 1985; Taylor 1989).. The articulations in question, furthermore, are not ready-made, but must be localised within practices.

Reflexive hermeneutics

Along with Kolb and Habermas we saw that Heidegger operates with a too close connection, indeed a one-way directedness, between the different layers of generality or meaning in modernity. Not without reason, when applied directly to social phenomena, such a procedure grants for a "bad social analysis".

Recall how Heidegger proceeds in order to situate his analysis as Being-in-the-world. He starts out with the things that are 'nearest to us' namely 'equipment': "The kind of Being which belongs to these entities is readiness-to-hand". Now, the Being of these entities is both a product of nature and of culture; the ready-to-hand is supported by nature as a means for caring for ourselves. Our caring for ourselves is grounded in our environment, which is neither purely nature nor purely culture; prior to these categorisations comes in either case that of Being. But the examples offered to us by Heidegger are always somewhat archaic in that they take this direct relatedness towards nature as their starting point: "The wood is a forest of timber, the mountain a quarry of rock; the river is water-power, the wind is wind 'in the sails'. As the 'environment' is discovered, the 'Nature' thus discovered is encountered too" (Heidegger 1962:100).

Even in the works on technology, this 'simple' relationship of work and nature is retained, although the storing up of the standing-reserve grants for the abstraction and covering-up of nature as its source. This relationship is also retained in the analysis of the mathematical projection and of physics as the paradigmatic science; it is always nature that is stored up through the framework of *Gestell* and the mathematical projection. I am not going to try and argue that this approach is wrong as such. But it is grounded in a different time and a different world than that of the present. In the words of Ulrich Beck: whereas we have moved on to second modernity, Heideggers analysis is situated within first modernity, and it does of course take its own time as its point of reference.

But how would it look if we returned to his procedure, but now situated it within second modernity? As a preliminary to the analysis of the following two chapters I will conceptualise the question in three steps, as differing but related thematic, each having to do with the production and distribution of knowledge. The first concerns the relationship between culture and nature, the second with the rise of biology, and the third with the up-scaling of the basic unities of research, the coming of "Big Science".

First and foremost: we cannot anymore, as did Heidegger, presuppose a simple relationship to nature. Whereas the meaning of the forest or the water-fall may strike us as immediate, this will not be the case with DDT, DNA, nuclear waste or nano materials. In the fifties, *biology*, apart from moving into the centre of attention in the scientific communities, also went from *analytic* to *synthetic* (Rheinberger 1997). Of course, this is not to state that *nature*; the materiality or even the *essence*, has been removed from the object of science. But the fact that the object is, to an increasing degree, also manufactured, involves that its meaning can no longer be regarded as simple to us.

The meanings from which we start our analysis of the ready-to-hand are themselves constituted by other processes of manufacturing. A case in point would be the application of sequencing machines to the work of identifying genes in the human genome. At the outset, these machines were not primarily intended for the human genome, but for the DNA from more simple organisms. Craig Venter pioneered their application to the more complex cases of humans. One of the problems he had to face in order to achieve this went as follows: although the sequencing machines had no problems identifying human DNA, it could not single out the genes that were effective in the production of specific proteins. In short, the machines would produce a large number of false positives (Davies 2001:56). Venter's solution consisted in feeding the machines with cDNA (complementary DNA) molecules that had already been in use by genetic engineers since the early 1970s. cDNA is distilled and stored in bacterial cultures from RNA that has already been expressed. Expressed RNA is transformed back into DNA using the enzyme reverse transcriptase. In this way, one would get to know the gene(s) that had been expressed, the information already being stored in the bacterial culture. Traditionally, these cultures had been used by engineers in order to produce *single proteins*. Venter's idea was to sequence the whole cluster of cDNA stored in the culture so as to end up with a so-called 'expressed sequence tag', EST for short. These would in turn be compared to bases from already identified genes from other species, so as to be able to

determine the exact location of the gene on the chromosome (*ibid*., 58). As the example shows, Venter's procedure took as its starting point materials (cDNA) that were already manufactured for use in a different context. In addition comes the sequencing machines, developed by Applied Biosystems, which again was the outcome of a rather complex procedure, involving venture capital and competition among biotech firms (Cook-Deegan 1994), genetic engineering as an established practice, and so on. The rhetorical question announces itself: what, in this context, is the being of technology, and what is technology of being? The question is no longer stable.

In many cases of late (second) modernity knowledge-based practices, the meanings from which we proceed at the outset, are already constituted by other meanings. In Latourean terms: they have already been inscribed. Hence, we get a sort of 'double hermeneutic' also in the case of the natural sciences. The meaning of the object does not readily announce itself; rather, it can be grasped only through processes of communicative and theoretical mediation and interrogation.

For the purposes of knowledge-based processes of production and distribution of objects, this will be one version of what Ulrich Beck terms 'reflexivity'; not primarily conscious reflection as traditionally understood within the social and human sciences, but rather meanings announcing themselves from within meanings originally perceived as simple. Taking the analysis one step further: where these meanings within meanings turn out to be of an altogether different character or quality than normally found within that practice, reflexivity utters itself as 'un-intended side-effects' (Beck and Bonss 2001) (Beck and Holzer 2004). A relevant example of this will be the appearance of ethical questions in the midst of what was taken to be purely 'scientific' or technological domains, as for instance seen in the case of stem-cell research and cloning procedures.

One reason for such a relocation of meanings may be found within the sciences themselves. Whereas physics has been *the* model of experimental science since the beginning of modernity, this situation may today be changing as biology becomes more important. Not surprisingly, therefore, strong institutional and intellectual forces try to subsume biology under the older paradigm of physics. But will biology, or the living itself, readily give way to manipulations structured after physics?

Biology deals with beings that are closer to, or even continuous with, our selves. As such, it is not that easily relegated to the domain of "outer nature", as may be the case with physics. As argued by Christoph Rehmann-Sutter, one important characteristic of biology is that it, in many cases (i.e., at least those dealing with animals and humans), has as its object lived processes, that are continuous or similar to the beings that we ourselves are: "…we are living organisms ourselves: we do biology essentially from the perspective of participant observers" (Rehmann-Sutter forthcoming). In classical terms (i.e. the Aristotelian conception of praxis): action that carries within itself an understanding of the values and goals of the action itself, may in many cases be seen to apply to biological development. In physics, however, the conception of *poiesis*, that of goal-directed action in which the final aim of the production is wholly external to the process itself, will in many cases be more applicable to the processes under scrutiny.

For the sake of the later description of biotechnological practices in first and second modernity, I will briefly remark upon one further difference between biology and physics. The difference in question is one that has been central in biology since its very inception, and which continues to play a central role, both methodologically and practically, that is, in the application, clinical or otherwise, of biological research. What I am aiming for, is the distinction between specificity and generality in the explanation of biological and physical phenomena (Mazumdar 1995). The conception of species specificity has been central to biological explanation at least since the time of Darwin, and it continues to delimit *and* promote the possibilities inherent in bio-technological interventions with the living. For instance, diphteria anti-toxin would be effective against diphteria toxin, and not against anthrax toxin. Differently, it would seem that many entities of physics, for instance neutrinos, would be the same no matter where in the universe they are encountered. Hence, while biology may posit global validity, this validity will in many cases be seen to differ from that encountered within physics. Perhaps we may state that biological knowledge is at the same time global and local, insofar as it will only allow for specific interventions, be they directed towards some micro-molecular entity, a species, an organ, a tissue or even an entire eco-system.

These two mentioned factors by themselves should indicate that meanings originally stemming from different contexts than the scientific or technological, will be more likely to announce themselves within these practices or discourses themselves insofar as they work

towards the standardisation and instrumental manipulation of biological processes. As shown by (Canguilhem 1991) and (Merleau-Ponty 1962), the life sciences are more liable to immanent critique than is physics. This, however, in no ways guarantee that this is the way in which present-day biological research is actually carried out:

Classical physics, here taken to mean physics up until Heisenberg and Bohr, would be grounded in a determinist and mechanistic world-view. After the Copenhagen interpretation of quantum mechanics, most physicists abstained from such claims to totality (Fjelland 2001). If such a claim is now dubious regarding physics, it will be even more so when applied to biology. Even so, there is no lack of scientists attempting such an undertaking:

"…eventually one may hope to have the whole of biology "explained" in terms of the level below it, and so on right down to the atomic level. It is the realization that our knowledge on the atomic level is secure which has led to the great influx of physicists and chemists into biology" Crick quoted from (*ibid.,* 87).

Hence, we see that the "paradigm" of classical physics has not been uprooted, and that it lives on also in the field of biology[11]. Still, the point is as follows: if this attitude would easily give itself to classical physics, it may be expected that the subject matter of biology resists such deterministic schemata of interpretation. In Fox Keller's view, present-day "gene talk" has taken on something very similar to what Georges Canguilhem termed "scientific ideology", and so runs the risk of countering it's own goals: "For if…the term *gene* may in fact have become a hindrance to the understanding of biologists, it has perhaps become even more of a hindrance to the understanding of lay readers, misleading as often as it informs" (Fox Keller 1995:148).

Even if we leave out the question of the epistemic correctness of Fox Keller's interpretation of biological genetics, the quotation still brings forth an important point: the goals and methods inherent in the practice of biologists cannot be regarded as external to the debate about their wider social responsibility. This is not only a question of responsibility corresponding to

[11] In fact, it may be argued that this is the *only* place where the ideology of classical physics continues to flourish. As described by Fjelland (*ibid.*): following the Copenhagen interpretation, few physicists today will claim that their models represent "reality in itself". The only scientific admission to reality we obtain through the use of instrumentation, models and theories. Furthermore, it is also questionable whether it is, as Crick claims, "the realization that our knowledge on the atomic level is secure which has led to the great influx of physicists and chemists into biology". As claimed by Kay (2000), Abir-Am (1982) and others, disappointment with the role of physics in the construction of the atomic bomb was one important reason for the flux of physicists into biology.

publicly provided funding; it is even more so a question of the social consequences of science; of the co-production of scientific and social order (Jasanoff 2004).

The above section provides a bridge to the last main development within the (social) role of science that is here to be remarked upon: the change from science as a relatively small-scale enterprise towards so-called Big Science.

With "small science" is meant scientific activity performed in a close relationship to experimentation, with the individual researcher as the central actor, and requiring relatively scarce resources in the form of funding, laboratory equipment, assistance and so on. As a result, responsibilities and rewards are relatively easily located within the scientific community as centred round the individual scientist. As will be seen, the early days of biotechnological research (i.e. first modernity), fit well within this description.

"Big science", however, remains an historical outcome of the efforts within the US weapon laboratories following the research efforts of world war two (Pickering 1995). Big science requires large teams of scientists and technicians, and correspondingly huge amounts of economical support. Its work may be divided and spread across huge distances of space. Hence, it requires bureaucratic organisations as well as well-defined hierarchies of order to function. By and large, this phenomenon has been reserved for the physical sciences (space programs, high energy physics…), but with the coming of the Human Genome Project, the question is legitimately posed whether biology has also taken an important step towards Big Science (Organisation for Economic Co-operation and Development 2003).

The significant point, which is yet to be described in some more detail, is this: biology has left the small-scale bench-style of its early periods, and entered upon new and complex ways of organising its activities. From holding a *relatively* autonomous position within academia in first modernity, in second modernity it finds itself within a rather complex organisational structure, consisting not only of the academic community; one in which the large majority of it's practitioners in the USA finds him or herself as somehow connected to corporate and high-risk capital investments.

It is developments like these that have led authors like Susan Wright and Sheldon Krimsky to talk about the academic-industrial complex of the life sciences, and to describe this new

"regime" as dealing decisive blows to the traditional research ethos of biology (Wright 1986; Wright 1994; Krimsky 2003).

Between ourselves and Heidegger then, we find at least three major significant shifts within the production of knowledge: 1) the upheaval of the simple relationship to nature, to some degree corresponding to the upheaval of the nature/culture-distinction as a *Basisunterscheidung* of first modernity (Beck and Bonss 2001). In short, we get 'knowledge processes processing other knowledge processes', and not only knowledge processes processing nature. 2) The replacement of physics by biology as "the" science, and 3) the replacement of big science for small science.

I now turn to a description of how these developments may be grasped in more sociologically oriented terms. I start out with a general description of the *Wissensansatz* of the theory of reflexive modernisation. As Beck's theory does not address the production of knowledge as such, I also address a number of other authors ranging from classical philosophy of science and epistemology to the broader field of social studies of science and technology.

2. Socialised science and social theories of science

Towards the end of the last chapter I described some central developments that have taken place in the relationship between science and society during the last part of the 20th century. In many ways, these developments may be seen as realisations and successes of the modern project: most parts of the western world are thoroughly imbued with the values, institutions and action patterns of science and technology. Decisions of broad significance are, by and large, based upon some specific type of knowledge; lay persons are bound to place trust in abstract expert systems, unable to perform basic activities without relying on the "black boxes" of engineers, scientists, medical doctors or lawyers (Giddens 1990; Wynne 1996).

Still, as also contained in the description of the previous chapter, it is not self-evident that science as a dominant social institution is prepared for its responsibilities. A situation in which scientific activities increasingly become intertwined with other institutions, as those of industry or commerce, demands other, more complex ways of understanding the social role of science than those contained within the classical ethos of research, like Mertons norms of communalism, universalism, disinterestedness and organised scepticism (Merton 1973). Other examples are the positivist doctrines of Ernst Mach and Claude Bernard.

The issue at hand is not just with the ethos of research, what Knut Erik Tranøy has termed the "internal norms of inquiry" (Tranøy 1976). More to the point, and still within the Tranøy's terminology, it is with the "external norms" of research: "the norms and values required to legitimate science policies" (*ibid*.). But we should expand our scope even further: the central issue is the basic concepts (internal) through which we organise, science and the ways in which these are justified and legitimated (external) in the face of *the applications and consequences* of science and technology, on society and on nature (Nowotny, Scott et al. 2001). These, I take it, should (optimally) be regarded both from the external *and* the internal perspectives. In spite of the success of the modernist program of knowledge and production, or, just as true, *because* of its success, socialised science also results in side-effects that were not considered in the original scheme. The central example in this respect may be the threat of ecological disasters resulting from human activities (Beck 1992). In medicine, the profession itself worries that the intrusions from other action systems may in the end turn out as disastrous for medicine itself:

"Physicians today are experiencing frustration as changes in the health-care delivery systems in virtually all industrialised countries threaten the very nature and values of medical professionalism…We share the view that medicine's commitment to the patient is being challenged by external forces of change within our societies", *Charter on medical professionalism* (European Federation of Internal Medicine, The American College of Physicians et al. 2002).

Furthermore: one has become aware that medical treatment itself does carry with it significant and concrete side-effects. In 1975, Ivan Illich' book *Medical Nemesis* stirred the medical community with its claims that medicine did more damage than good to society. Illich introduced the concept of *iatrogenesis*, by which he meant to signify physician-induced illness, or even death. The conception of iatrogenesis covered three levels: 1) the clinical, 2) the social, and 3) the cultural. The analysis of iatrogenesis on level 1) took its main premises from the medical litterature itself (medical journals, medical statistics). It did not by itself raise claims about empirical phenomena that were not already verified; it merely synthesised them in a new way, and so provided an argument that was hard to refute on a wholesale scale. As it turned out, levels 2) and 3), were of a more speculative kind, dealing with what Illich termed the „medicalisation of society and culture". „Medicalisation" means something like „the illegitimate transformation of social, political or cultural problems into medical problems" (Aasland 1992). Although met with stark opposition, first and foremost because of its onesided condemnation of technological medicine, the claims put forward in *Medical Nemesis* about *clinical iatrogenesis* (level 1) may today be considered mainstream knowledge (Light and Aasland 2003).

This chapter will start to adress the ways in which we may grasp some of the social tensions created by science and technology. I have already indicated the reliance upon the work of Heidegger and Beck. This in itself should require no further explanation: both deal with science and technology[12]. Still, there are other players in the field that may be considered even more relevant to the project at hand, and the choice of method requires some justification.

Although it may have started out as such, with the *Risk Society*, Ulrich Beck's theory of reflexive modernisation is not primarily about science (Lash 1992). In more recent times, the theory has instead come to occupy itself with the consequences of globalisation. Still, central

[12] Admittedly, the combination of these two thinkers, so different in most ways, may seem strange. Still, I hope to convince the reader that it may be a fruitful synthesis. Furthermore: I will point to similarities in their views on how to live with technology that make both thinkers amenable to bypass the worn-out opposition between modernist and postmodernist theories of technology.

parts of the theory concerns itself with modern society *qua* knowledge society. Before I continue to consider other theories, I will give a brief summary of what I take to be the central points of the *Wissensansatz* of Beck's theory.

According to the theory of reflexive modernisation, three socio-historical stages are decisive to the present state of social organisation: traditional society, modern society and reflexive modern society (second modernity/late modernity). The first two categories form one of the basic presupposition of classical sociology; namely the transition from *Gemeinschaft* to *Gesellschaft* (Tönnies). For our purposes, the significant moment here is the transition from traditionally situated and mediated action to knowledge-based and institutionalised action through expert knowledge (Giddens 1990; Beck, Lash et al. 1996).

In pre-modern society, tradition is the basic source of legitimacy. In modern society *knowledge*, to a large extent, replaces tradition:

"Der Wissensansatz reflexiver Modernisierung lässt sich –stark vergröbert – folgendermassen verbundeln. Erstens: Je moderner eine Gesellschaft wird, desto mehr Wissen erzeugt sie über ihre Grundlagen, Strukturen, Dynamiken und Konflikte. Zweitens: Über je mehr Wissen aber sie über sich selbst verfügt und dieses anwendet, desto nachdrücklicher wird eine traditional bestimmte Konstellation des Handelns *in* Strukturen aufgelöst, und an ihre Stelle treten eine wissensabhängige, wissenschaftsvermittelte Rekonstruktion und Restrukturierung sozialer Strukturen und Institutionen" (Beck, Lash et al. 1996:290).

In a phenomenological and hermeneutic language: important premises of action have been removed from the life-world, in which *Gemeinschaft* has its basis, and it has been replaced by organised and knowledge-based structures of action; i.e. by what is here called action-systems. This is a relative, not an absolute difference; also traditional society was to some degree specialised, and tradition continues to carry meaning also in modernised society.

The significant transition in terms of action is that it is connected to and situated upon bases of knowledge. This connection changed the whole conception of knowledge and action; what was previously *Art* was to become *Science*, see for instance (Bernard 1957; Heymann and Wengeroth 2001). This also changed the life-worlds and their conditions in significant ways: although ‚specialised', the different types of knowledge in pre-modern society were part of a natural order, handed down by tradition. In modernity, the „natural" is constructed in a very specific manner, as it is turned into a scientific concept. In significant ways, the „natural" is

now constituted by its opposition, through the reflective questioning of tradition and nature, and thereby also the decisive elevation of culture to the role of the master of nature. Knowledge is no longer bound to concrete persons within specific points in time and place, but is abstracted into systems in which it is acted out by professionals. The effectiveness of modernised knowledge has therefore come at a price: the dis-embedding of knowledge (Giddens 1990) from the life-world and its transposition into action systems. ‚Reality', in terms of the scientific object or in terms of wider concepts like ‚health' or ‚justice' is to a large extent removed from the action domain of the life-world, now to be acted out and re-embedded by the expert/the professional.

But, says Beck, development does not halt at this:

„Wissen erzwingt Entscheidungen, öffnet Handlungssituationen. Die Individuen werden freigesetzt aus Strukturen, und sie müssen unter Bedingungen hergestellter Unsicherheit in Formen und Strategien „reflektierter" Modernisierung ihre Handlungssituation und Identität neu definieren" (Beck, Lash et al. 1996:290).

This is the thesis of *individualisation*: members of society come, to an increasing degree, to rely upon their own values as the basis of choice. When applied to knowledge: knowledge becomes, to an increasing degree, negotiable. Also expert knowledge may be questioned, either because of its social consequenses, because of differing expert opinions, because of lay-peoples increasingly high level of education, or because of new and increased flows of information (Lash 2002), and so on. The central claim, first conceptualised in Beck's *Risk Society*, is that socialised knowledge, to an increasing degree, turns up in the form of uncertainties and risks (Beck 1992). For instance: clinical judgement is increasingly caught up in evaluations of risks for the patient. This is not least due to an expansion of the medical system into new areas: preventive medicine by necessity deals in degrees of risk and uncertainty (Clayton 2003; Elmore and Gigerenzer 2005), insofar as it deals with that which is *not yet*: high blood pressure, cardio-vascular disease, susceptibility to inherited conditions and so on.

At this point, I will take the time to pause upon a matter of dispute among theorists of reflexive modernisation that has been mentioned in the introduction and that will be of importance for the further analysis. Hermeneutically inclined theorists of reflexivity, particularly Scott Lash and Brian Wynne, argues that the above quoted account of knowledge and of individualisation is grounded in a „contractual" image of social dynamics in general,

and of *trust* in particular (Lash 1992; Beck, Lash et al. 1996; Wynne 1996). A similar critique has been put forward by Michel Callon (Callon 1999), but I will concentrate mainly on the critiques of Lash and Wynne. Individualisation, so the critique goes, happens because lay persons observe the inner inconsistencies in the rationalities of experts, and so come to draw the conclusion that science cannot be trusted to deliver the goods anymore. On this account, individualisation is a matter of a rational choice made by social agents when they see that expert systems can no longer fulfil their part of the contract with society, i.e. to provide secure knowledge. The critique is directed at both Giddens and Beck, who are both deemed to present cognitivist and rationalist versions of reflexivity[13]. The critique may have something going for it in the case of Giddens, but in the case of Beck it is definitely *wrong*. Indeed, as described in the above passage, individualisation and the diversification of rationalities do take place (more or less) at the same time as second modernity unfolds. But their inner relationship is more complex than portrayed by Lash and Wynne.

Whereas modernity ‚opened up' traditionally situated patterns of action organisation and reposited them within knowledge-based structures and institutions, reflexive modernisation in *its* turn re-opens these action structures and institutions. The fundamental difference between the two stages lays in the claim that whereas the transition from traditional to modern society to a large extent was *intended*, the transition from modernity to reflexive modernity *is not.* It is rather a consequence of the cumulative, non-intended side-effects of action and production in modern society:

(1) Je moderner eine Geschellschaft wird, desto mehr Nebenfolgen erzeugt sie, die, in dem Masse, in dem diese (an)erkannt werden, die Grundlagen industrieller Modernisierung in Frage stellen.
(2) Auch Nebenfolgen sind also gewüsst. Die Frage ist nur: von wem und auf welcher Grundlage? Selbst der Begriff „*latente* Nebenfolge" meint nicht kein Wissen, sondern *ein* Wissen, dessen Anspruche allerdings *umstritten* sind. Die rede von „Nebenfolgen" kennzeichnet also einen Wissenskonflikt, einen Rationalitätskonflikt: die Ansprüche verschiedener Expertengruppen treffen aufeinander sowie auf die Ansprüche des Alltagswissens und des Wissens sozialer Bewegungen...
(3) Dieser Konflikt verlauft *nicht* in klaren und eindeutigen Zuordnungen von Wissen und Nicht-Wissen – entweder im Sinne der Expertenrationalität oder der Expertenkritik sozialer Bewegungen...
(4) So diffus dieser Konflikt erscheinen mag, er entbrennt um ein Ziel: die Verteidigung oder Überwindung institutioneller Experten-Konstruktionen des Nicht-Wissen (-Könnens) über die „Neben"-Folgen organisatorischen Handelns für andere (Personen, Gruppen, Institutionen, Teilsysteme, Länder, Erdteile)... (Beck, Lash et al. 1996:298-299).

[13] In this context, "reflexivity" does not mean "self-reflection" as for instance found within philosophical theories of modernity. It is a rather wide term that may be taken to mean something like "the transforming forces of second modernity". Especially in Beck, it is institutional rather than intellectual, and it is first and foremost promoted by the non-intended side-effects of the modern mode of organising action and production (Beck and Holzer 2004).

Individualisation and reflexivity happens, not simply because expert knowledge and authority is rationally questioned, but rather because deeper changes in the organisation of action and production are *not* percveived (Beck and Holzer 2004). There is an increasing gap between the institutions of modernity and the reality (whatever that may be) which they are set to regulate. True, this promotes a widening gap between knowledge and reality because most of the time expert knowledge proceeds more or less according to old modern recipies (Beck 1993). This, however, is more of a *consequence* than a „cause", or promotor, of the deeper *Strukturwandel* of second modernity.

In the present project this will become clear from the comparison between immunology (first modernity) and genetics (second modernity), where it is seen that much more is at work (and at stake) than simply the rational questioning of expert rationality. Genetics, it is argued, promotes individualisation because it lacks some of the action-organising capabilities offered by immunology (and bacteriology). Significantly: whereas immunology and bacteriology issued in almost immediately deployable techno-medical *objects*, i.e. therapies, this is not the case with genetics. Genetics is hampered by a „therapeutic gap", i.e. well-developed *diagnostic* capabilities that are not backed up by corresponding therapeutic measures. In short: as we speak there are practically no efficient cures for genetically diagnosed diseases, and so there are no techno-medical objects in which to *delegate* action-organising capabilities. In stead, the genetic diagnosis typically issues in terms of *information*, to be deployed in the best (most rational) manner possible by the patient. This is a deep transformation in the action-organising capabilities of the medical system promoted by a number of factors, but it is not a matter of chosen development instigated by the social agents (patients) themselves.

The main reason why Lash and Wynne do not perceive this state of affairs, I take it, is their endorsement of „ethnometodology", focusing mainly on the cultural aspects of reflexive processes. Interesting and relevant as that may be: it does not suffice as a substitute for the institutional analysis undertaken by Beck. One further reason why Lash and Wynne do not perceive of this state of affairs, is that they (especially Wynne) seem to pose the wider sociological question of *social integration* almost exclusively in terms of *trust*, which is a constituent of micro-sociological or ethnomethodological preferences. Such a move, however,

overlooks not only the institutional perspectives, but also, as indicated above, the *material aspects* of social organisation.

It is not well conceived, therefore, when Lash and Wynne accuse Beck's theory of being „cognitivist" or „rationalist". They are right when they say that there is a lack of (specifically) hermeneutic elements as well as a reflection upon cultural methodology in Beck. This, however, is merely to state the obvious, and is not really a „methodological" consideration. Indeed, Beck's theory is interpretatative, and as such fully amenable to hermeneutic reflection, as I intend to show in some more detail. That hermeneutic reflection, however, will not be microsociological, but is rather to be found at a mid-range level. There is, in general, no reason to assume that hermeneutic reflexion must be exclusively micro-sociological or ethnographic. This much should be clear from the previous account of Heidegger's philosophy of technology.

I will now start to turn to the question of the socio-material organisation of society in some more detail. I do this by first turning towards the theory of science.

Theories of socialised science

Before continuing the line of reasoning from the last section, I will start out by giving a brief account of some developments within the philosophy of science in the last half of the 20th century. One important reason for doing so, is to strengthen a point that has already been pointed out in connection with the analysis of Heidegger: philosophy of science should, in order to maintain its relevance, let itself inspire by sociological and historical analyses and methodologies. Furthermore, the analysis is meant to single out the more relevant and interesting works in the field. As the turn towards sociological and historical analysis indicates, these are not to be found within the mainstream philosophy of science.

In the 1960s, philosophers like Popper, Kuhn and Lakatos sought out alternative explanations for scientific rationality in order to substitute the long prevailing account given by logical positivism. Along with Lakatos, Kuhn acknowledged the central role of historiography to the philosophy of science. The logical positivists, but also Popper, had sought out rigorous and a-historical standards of rationality that may have gone well with logic, but which nevertheless gave poor descriptions of the ways in which scientific research was actually carried out. The most radical conclusions to be drawn from the critique of positivism seemed to come from

Thomas Kuhn. In *The Structure of Scientific Revolutions*, he suggested that scientific progress was not a matter of linearly increasing rationality, but rather the result of scientific work carried out within pre-established "paradigms". Paradigms were meant to signify contextually and historically situated frameworks of theory, instrumentation and research methods established through so-called "scientific revolutions". Work within a paradigm, "normal science", could only have its degree of success measured according to the standards established through these specific rules or frameworks, and so it made little sense to compare one paradigm to otherwise situated research paradigms with respect to truth value or verisimilitude.

According to the normal reading of the history of philosophy of science, Kuhn may indeed be displayed as breaking radically with certain elements of the tradition. Still, already before the book was published, Karl Popper's student Paul Feyerabend had criticised it for its conservative outlook on research (Fuller 2000). In Kuhn's description, it seemed that the rules of each paradigm were almost carved in stone, and so it would be futile for the "normal" scientist to criticise the present paradigm in order to search for better solutions, less even so try and relate research to normative or political issues. Indeed, Kuhn's book could be read as a return to historicism, vehemently criticised by Popper in his *The Poverty of Historicism*.

Be that as it may. Central points of Kuhn's critique should be taken seriously, significantly the need for placing science within its historical and social setting, so as not to lose sight of the landscape while reading the map (the philosophy of science)[14]. One valuable outcome of this has been the realisation that science can indeed be studied by the use of methods taken from the humanistic and social sciences. This is not a mere matter of theoretical or reflexive improvement: the socialisation of the sciences so dominant in second modernity corresponds temporally to the realisation that natural science should be studied by the use of socio-historical methodologies, which again coincides rather nicely with the re-structuring of the nature/culture-divide described in the previous chapter, and so the relationship is a circular one[15].

[14] Indeed, this point would be better made with reference to Feyerabend, whose analyses were indeed better informed by and situated within, the history of science. However, the term Post-Kuhnian philosophy of science is already established (Nydal 2002).

[15] This is not to say that such tendencies are unique in the history of modern science. But an instance like the debates concerning science and ideology in the 30s and 40s cannot be considered here due to the scope of the analysis.

As this is a work in the hermeneutic tradition, I will briefly consider the position of hermeneutics in relation to the above-mentioned developments.

In the case of *modern hermeneutics*, historicity was always essential (Gadamer 1960; Heidegger 1962; Taylor 1971-1972; Ricoeur 1981; Taylor 1985). Still, it seems that hermeneutics as practiced by prominent thinkers like Gadamer, Taylor and Ricoeur has placed itself in a rather awkward position by remaining with the social and human sciences only[16], and by relegating the natural sciences to analytic philosophers and the (few) natural scientists that found the occasion and the interest to rise their head above the laboratory bench and consider the wider function of their science. The problem is primarily historical and not methodological. We know this from reading Husserl, Heidegger and Merleau-Ponty, who all, in an earlier stage of modern hermeneutics, concerned themselves with different parts of the natural sciences. There has, of course, also been exceptions to the rule, and phenomenologists and hermeneuticians have indeed entered upon the study of the natural sciences (Ihde 1979; Dreyfus and Dreyfus 1986; Fjelland 1991). Still, these remain exceptions.

One important reason why the followers of Husserl, Heidegger and Merleau-Ponty have swayed from this path goes as follows: a main concern of writers like Gadamer, Taylor and Ricoeur, but also Habermas and Apel, has been to defend the social sciences from illegitimate intrusions from methodologies shaped after the model of physics. Hence, they have been more than happy to leave out a number of questions central to the *Wirkungsgeschichte* of modern science, to the philosophy of science, and thereby also to hermeneutics itself. This they did by endorsing the position of metodological dualism. In short: Natural science is deductive nomological, human and social sciences are interpretive (Apel 1979)[17]. In Norway, Hans Skjervheim was a prominent protagonist of this view.

If we for the moment leave out the highly heterogeneous group of scholars that may fit the description „post-Kuhnians“, the bulk of 20th century philosophers of science who have concerned themselves with the natural sciences have belonged to the analytic school of thought. Post-empiricist thinkers like Davidson and Quine have occupied themselves with

[16] For a critique of Taylor's position, see (Geertz 1994). For a more general critique of hermeneutics, see (Fuller 1988).

[17] Karl Otto Apel once gave a talk at the faculty of natural sciences at the University of Bergen. After listening for two hours, a member of the audience raised his hand and commented: "So, you're a positivist then". Apel, who surely must have asked himself if this person had been listening at all, furiously denied this. But, from the point of view here taken, the interlocutor was in his full right (I heard this story from Ragnar Fjelland).

discerning the objective presuppositions inherent in any language, so as to secure the position and authority of the natural sciences, especially against the threat coming from the incommenurability thesis: paradigms are inherently different and cannot be compared, hence they are also incommensurable. These positions will not be considered here. Suffice it to notice that they: 1) do not recognise the social sciences as rational enterprises proper, hence they are not capable of appreciating the relevance of these disciplines to the study of the natural sciences; 2) fall within what we, following Ian Hacking (Hacking 1983) may term „representationalism". Within the representationalist school, Hacking says, the task of philosophy of science is to carve out the logical structures of the natural sciences, even if the conceptual schemes thereby constructed corresponds rather poorly with the ways in which science is actually practiced.

A powerful critique of representationalism that should also be mentioned is (Rorty 1979), not least because of its reliance upon Heidegger. Unfortunately, Rorty's critique does not point us towards any interesting alternatives, remaining as he does within the abstract conception of „conversation" as substitute for the „reality" defined by the representationalists. Commenting upon James Dewey and his present-day follower, Rorty, Ian Hacking remarks that „He [Dewey] should have turned the minds of philosophers to experimental science, but instead his new followers [Rorty] praise talk" (Hacking 1983:63). Indeed, the neglect of experimentation is only the starting point of Rorty's ignorance. If representationalism is a problem worthy of serious discussion, surely it must have some relevance also *outside of* the philosophical discourse? When philosophy (or any discipline) has nothing to turn on except itself, it verges towards the pathological. The quality of *Philosophy and the Mirror of Nature* thus seems to exist within a rather limited and, in a social context, idiosyncratic field of reference. In passing judgement upon its own discipline (which it performs with excellence!), it neglects the possibility that somewhere within this field, there might still be something of value and relevance to the (transdisciplinary) study of the sciences and society. The result is that any claims to validity is relegated to the division of labour between the single disciplines, informatics, psychology, linguistics and so on, an (anti-)reflexive move to which Steve Fuller has given the proper name of *The Rorty Fallacy* (Fuller 1988). One possible reason for this failure, which will be described later in a slightly different context, is Rorty's fundamental reliance upon postmodernist, aesthetical categories. As will be argued, such a notion also disfavours the notion of aesthetics, insofar as aesthetics seem to become deprived of any rational content.

To sum up, then. The two main schools of philosophy of science, the analytical and the continental have, each in their way, taken on courses that make them ill-suited to the analysis of socialised science as here described[18]. To put it with C. P. Snow: the problem of the two cultures in science has been reproduced within the philosophy of science, and so it has ended up as incapable of conceptualising one of the main problems in the modern production of knowledge (Snow 1959). That this phenomenon is not simply existing in the heads of philosophers should furthermore have been amply confirmed by sharp level of conflict of the so-called science-wars, in which humanists and social scientists (social constructivists, ANT, STS..) stood against natural scientists in a debate about the basis and rationality of science (Fuller 2000).

We must, then, turn towards „post-Kuhnian" theory of science for analyses more relevant to the present project. First and foremost, we need analytical tools that do not easily accept the divide between the natural and social/human sciences. This is directly connected to the destabilisation of the nature/culture divide. A simple relationship to nature cannot any longer be presupposed, and culture cannot and should not, when dealing with science and technology, be regarded in separation from what we term „nature" (Lau 2001). Furthermore, the turn from representationalism and towards science as practice entails that temporality is taken seriously, not primarily as an object of analysis in itself, but as constitutive of the workings of science (Callon and Latour 1992; Pickering 1992).

I will now consider in more detail some important points from studies of science and technology, first and foremost the works of Bruno Latour. As already described, of primary importance are the attempts at overcoming and rethinking established nature/culture divisions, as we find them in the theory of science and in the social institutions. But it is also important to get a grasp of how Latour displays the manners in which the the scientific object is disseminated in society after its solidity, its „hardness" as a fact, has been established. I am in no way aiming to give an exhaustive description of the highly composite and heterogeneous field of science and technology studies here, nor to give anything like a complete exposition of any single writer, significantly Latour. The main point is to position the present analysis methodologically, and in that process also to absorb some lessons that should be drawn from

[18] Radnitzky (1968) and (1968a) gives an instructive overview of the topography here referred to.

STS and ANT. Although in other places I have adressed other parts of STS, significantly those having to do with expert/lay divisions and trust, I here address the branch of laboratory studies.

Framing nature and culture

Taking as our staring point an article from the (in-)famous „Chicken debate“ in (Pickering 1992). Latour, together with Michel Callon, argues against two positions in particular. One the one hand, realist and representationalist interpretations of science, in which nature is seen to be the „cause“ of true knowledge. In the above exposition of the two traditions in philosophy of science, this would correspond to central trends within the analytic tradition: truth is legitimised with reference to nature, and false knowledge is explained as a consequence of mistakes on the part of the knower, hence relegated to culture. On the other hand, we find early versions of science studies, the sociology of scientific knowledge (SSK), in which culture is not invoked in order to explain scientific mistakes, but rather in order to explain how science and its product, true knowledge, is formed and performed. On this account, supposed to constitute a *symmetrical* relation between true and untrue scientific knowledge, nature is a product of social interest, of *culture*:

”What sociology of science provides is a third method, no longer subservient to accounts of the work of the scientists and technologists and the stories of philosophers but rooted in a special understanding of social life” (Collins and Yearley 1992).

But if we endorse this point of view, we are committed to error, as the central point is not to explain culture from the point of view of nature, nor vice versa. Latour’s point is that falling down on either of these poles won’t get us anywhere, as it is exactly the construction of these poles that needs to be explained in the first place:

“We take as progressive any study that simultaneously shows the coproduction of society and nature. The phenomenon we wish to describe cannot be framed from the two extremes on the SSK yardstick – nature out there and society up there – since on the contrary, “natures” and “societies” are secreted as by-products of this circulation of quasi-objects” (Callon and Latour 1992).

In the previous section, I briefly touched upon the methodological necessity of a descriptive language that clearly distinguishes itself from that of the scientist. We can now start to see the appropriateness of such a move: culture and nature are co-produced in the scientific process, and so there are two starting points that cannot be accepted: 1) that of the scientist, who has

been socialised into a language framed in the tradition of scientific realism (this is not to say that the single scientist actually has to be a realist), or 2) that of the social and humanist sciences, in which the social is invoked to explain the occurrence of natural phenomena. Latour is up against the two cultures of science, and so he sees the need for constructing a new descriptive language.

The attempt of such an overcoming, in the form of the "theory" of the actor-network, is therefore not supposed to form a new theory as such, but is rather to be seen as a form of provisory ontology (Nydal 2002) in which new descriptions of the coproduction of nature and society are constantly sought out. The perhaps most radical move taken by the theory is the transformation of SSKs methodological principle of symmetry to a general ontological principle. In SSK, the principle of symmetry was invoked through the methodological decision of explaining false scientific statements on a par with true statements (Bloor 1976). In the radicalised version of the actor-network theory, the decision becomes an ontological one, insofar as non-humans are treated on a par with humans. Hence, a scallop may be seen as no less an active agent ("actant", "hybrid", "quasi-object"…) than a fisherman or a marine biologist (Callon and Latour 1992). The main reasoning behind such a seemingly absurd move is to avoid classical explanations described above, in which one or the other pole on the nature-culture axis is regarded as causally dominant. In actual practice, however, things do not happen like presupposed in classical description: the movements of the scientist are just as determined by the materials/objects under scrutiny as the other way around, and frequently the language of the scientist or the engineer will also reflect this state of affairs. Therefore, the latter will be likely to grasp the new situation faster than the social scientist (*ibid.*).

Somehow, we need to get to the Archimedean point in which the scientist and his object reciprocally define and are defined by each other. For this specific purpose, the traditional social analysis will always come too late. In the significant cases where scientific breakthroughs are also social breakthroughs,

> "The exact sciences elude social analysis not because they are distant or separated from society, but because they revolutionize the very conception of society and of what it comprises. Pasteurism is an admirable example. The few sociological explanations are feeble compared with the strictly sociological master stroke of the Pasteurians and their hygienist allies, who simply redefined the social link by including the action of the microbes in it. We cannot reduce the action of the microbe to a sociological explanation, since the action of the microbe redefined not only society but also nature and the whole caboodle" (Latour 1988:38).

Now, let us consider in some more detail how Latour proceeds to escape the dilemma of social science. To use an example: It is easily understandable when we state that this or that (social) rule, like in Wittgenstein's language games, determines the use of some object, as for instance the two workers building with slabs described in the beginning of *Philosophical Investigations*. But we could also turn the situation around, and state that the slabs, their material composition, in important ways determine the actions of the two workers. If the materials were different, say, made of a stone that broke more easily, this would change the practice of the two workers, and so also the rules by which they abide (we easily see that the *shape* of the slabs cannot be used as example in this way, as shape is also a matter of culturally inflicted attributes. The material composition of the slabs however, is not: we may imagine similar building practices (the two builders are globalised workers!), but operating within different natural environments where the same materials are not available).

Just as social rules may facilitate and hinder certain modes of action and experimentation, so the material resists or gives in to the force of other actants, be they human or non-human. In this way, the question becomes one of describing the relations and constellations among actants rather than of ascribing causal primacy to "nature" or "culture" on the basis of old habits of speech: "The real is not one thing among others but rather gradients of resistance" (Latour 1988:159).

In this perspective, it also makes sense if we state that the scientist or the engineer (or the farmer, for that sake), actually *negotiates* with the materials. The laboratory has come to constitute the privileged site of such negotiations in our society. Of course, such "negotiating" is not undertaken in order to reach a reciprocal agreement with the material, say, microbes, the point is to come to terms with the material world in such a way as to render it *controllable*:

> "…in every laboratory…phenomena are finally made smaller than the group of men who can dominate them. If this is regarded as simplistic, it is because of not understanding the extent to which the strategy of constructing laboratories obeys this simplification" (Latour 1988:74).

In order to describe the process by which phenomena are made to obey the commands of the scientist or the engineer, Latour invokes the textual metaphors of *inscription* and *translation*

(Latour 1986). In the laboratory, the complexity of the world is translated into human terms by the use of inscription devices; instruments and machines are deployed by the experimenters in order to produce measurements, graphs and numbers that may, in the last resort, serve to stabilise the scientific object, to establish it as a fact. It is this process that, in *Laboratory Life*, is described as the production of facts, and it is during this process that inscription takes place; the object and the scientist are simultaneously inscribed during experimental activity; when the object resists or gives in to some manipulative action, the researcher is also transformed in the process, insofar as he is constrained (Galison) or facilitated in his/ her movements.

This entails a process of combining phenomena that, initially or historically, had not yet been connected into stable (in-)formation. Stabilisation means that the information in question may be confirmed also in different contexts: first and foremost other laboratories, but also by other actors, for instance medical doctors or apothecaries, taking part in the same network of actors, what Latour (borrowing from Mary Hesse) terms "acting at a distance" (Latour 1987). Hence, enormous amounts of information are comprised into what eventually becomes a fact, typically represented by the scientific article. This, then, is one essential part of the process of translation: that ways of acting thinking and writing that were previously not related in any strong sense of the word, are now comprised, i.e. "black-boxed", in the established scientific fact. Once a fact has been thus established, through repeated experiments, criticism from colleagues (peer-reviewed) and in the end been given general acceptance within the scientific community, the translation process is completed. This means that all the activities undertaken to establish the fact are no longer necessary, a short reference to the relevant fact, maybe also to its authors, is sufficient. At this point, the world has actually been transformed; at least the world of the scientists concerning themselves with the field in question. The next step, usually ignored by philosophers of science, consists transporting the fact out of the laboratory or the factory and into a more or less stable network of actants. This takes *work*, in which other actants are enrolled in the network of the laboratory:

> "papers, laboratories, new objects, professions, interest groups, non-human allies – so many, indeed that if one wished to question a fact or to bypass an artefact one might be confronted with so many black boxes that it would become an impossible task: the claim is to be borrowed as a matter of fact, and the machine or the instrument put to use without further ado. Reality, that is what resists all efforts at modification, has been defined, at least for the time being, and the behaviour has been made predictable, in certain ways at least" (Latour 1987:179).

In this way, translation is not only linguistic; it may entail serious re-structuring of the socio-material order, in so far as that which was previously heterogeneous and non-controllable phenomena are now seen to be controllable, but only on the condition of first passing through the laboratory, then through the wider network. In the case of Louis Pasteur, the negotiations with the microbes in the end resulted in "a new object that retranslated the disease [anthrax] into the language of the laboratory" (Latour 1988:76). This object was next transformed into a socially powerful fact through Pasteur's alignment with the hygiene movement.

In some important cases therefore, the production of the fact does not halt at the doorstep of the laboratory; the fact may indeed transform the world. In order to achieve this, it is necessary that also other institutions are enrolled in the network. It is an old miscomprehension of the representationalists that scientists produce facts, and that true facts (mysteriously) find their way also into society at large (mainly because they are true). The point is that a whole range of mechanisms are also necessary in order to socialise the fact on a broad scale, so as not only to change the world of the scientist, but also that of the politician, the lawyer or the lay person. These translations take *work*. In *The Pasteurization of France*, this is demonstrated by portraying Pasteur as a master of being at the right place at the right time, possessing the right kind of knowledge. (In Latours story) Pasteur moves between disciplines and social groups (most significantly that of the hygienist movement) in such a way as to enrol many different actors (also the microbes) into one network, which language is that of the laboratory and experimental bacteriology. In other words: Pasteur skilfully responds to differing social needs by the construction of a language and a practice of which he himself is the master[19].

Explaining, understanding and...

Let me now continue by explaining what I see as short-comings in Latours approach. The critique mainly turns on questions of the language deployed in the ANT analysis, but clearly the language itself is not the main issue. The language issue relates to the larger framework within which the analysis takes place, and so the question is ultimately one of self-reflection (Callon and Latour 1992), or, even more to the point: reflections on the *pragmatic* aspects of one's own framework.

[19] According to (Fuller 2000) this line of reasoning applies equally well to the success of the actor-network theory and its authors.

Speaking from hermeneutics, I argue that the Actor Network relies upon insufficient notions of action and (human) agency, which in the last resort may issue in a language ill suited to deal with some of the normative issues raised by the modern production of knowledge. The language deployed by Latour renders his analysis unstable, a state of affairs which may very well be intended by Latour himself, but which may easily lead to bad interpretations. In particular, this is connected to a lack of reflection upon action and (human) agency, which issues in a relation to the subjects/objects of study most peculiar to an anthropologist (such as Latour).

Centrally, I argue, and here I also include authors like Andrew Pickering and Karin Knorr Certina: these authors, for all their emphasis upon "contextualising knowledge", frequently operate with strangely limited notions of contextuality. This shortcoming is directly coupled to insufficient *articulations* (Taylor 1985b) of agency. Within contextualist conceptions of knowledge, rather a lot comes to rely upon the descriptions given and upon the understanding of agency brought into the analyses. Essentially: what does it mean to be an agent or an actor within a *context*?

In the rest of this chapter I will therefore try to clarify the meaning of „analysing science as a social institution". The main point is to position the analysis in relation to science studies. In the next chapter I will try and develop a hermeneutic version („reflexive hermeneutics") of science studies based upon interpretations of Heidegger's philosophy of technology and Beck's analysis of reflexive modernisation.

A distinction that has been central to the philosophy of science as described above, is that between explanation and understanding (von Wright 1971). Typically, the natural sciences „explain" whereas the social and human sciences „understand". Nevertheless, the social sciences, if not the humanist sciences, are not alien to the undertaking of explaning social forces. We may think of Max Weber's analysis of the growth of capitalism, in which protestantism is invoked as *explanans* and capitalism as its *explanandum*, or of Durkheims functionalist explanation of religion. But what can it mean when we state that social scientists „explain" or „understand" the works and actions of natural scientists?

Let me start out with an interpretation that must clearly be wrong:

It cannot mean that the social scientist ascribes laws, or social explanations similar to those sought out in the works of natural scientists, to the actions of the scientist himself. This strategy, says Latour, has been attempted by early sociology of knowledge (SSK), and it has failed: „The issue is not to explain the natural sciences by using social sciences“ (Latour 1988b). Rather, Latour's strategy consists in displaying the *work* inherent in the socialisation of facts and artefacts, especially those with a strong explanatory and institutional power, for instance the central dogma in the introduction to (Latour 1987). The strategy is somewhat reminiscent of that of Ludwig Wittgenstein, when he states that we have to give up explanation and let description take its place (Wittgenstein 1953). Explanations, says Latour (and Wittgenstein) are inherently reductionist, and so stand in constant danger of reproducing the very same regimes they are about to criticise. Comparing his own strategy of „irreductionism“ to that of scientific explanation, Latour writes that:

„...the first starts with *equivalences* without telling through which instruments and through which metrology these equivalences are obtained; the second starts from translations and tries to present the work of *rendering elements equivalent* by setting up new instruments and keeping long metrological chains in alignment“ (Latour 1988b).

Latour then sets out to establish more „equivalent“ ways of displaying the work of natural scientists and engineers. For this purpose, he sees it as necessary to establish a wholly new language, one independent of that deployed by the scientists themselves: „...to explain the science of the Pasteurians, we must describe it without resorting to any of the terms of the tribe“ (Latour 1988:8-9). Why does Latour, an ethnomethodologist, see it necessary to go to such lengths to distanciate himself from the agents he is describing? First of all, let's specify the question somewhat more: in many of his books he does indeed bring quotes from his agents. Hence, he does rely upon basic modes of understanding action, what hermeneuticians term prejudice (*Vorurteile*) (Gadamer 1960). What he refuses to consider, however, is the role of scientific knowledge and prejudice about the world, a large part of which consists in *explanations*, and these are to be shunned by all available means: „we will carry with us no preconceptions of what constitutes knowledge“ (Latour 1987:13).

Similar attempts has, as is well known (certainly also to Latour), been attempted carried out through the behaviourist program adapted to the philosophy of science (Naess 1936) and it has been amply demonstrated to fail in most respects, significantly because it does not make

explicit its own preconditions (Skjervheim 1959), hence also its role within the social scene of which it is part and which makes up the necessary frame of reference for any scientific activity whatsoever. This was the main topic of discussion in the biggest dispute in the philosophy of science in the 20th century, the positivism debate. It is also, within the philosophy of science as well as the sociology of knowledge (for instance Karl Mannheim), the old question of *reflexivity*, which is indeed an important part of the framework within which Latour is broaching the subject (Latour 1988b; Callon and Latour 1992).

One reason has already been mentioned: Latour regards the social sciences as much a part of the problem as he does the natural sciences: „...we strongly reject the helping hands offered us by the social sciences; on the contrary, we consider them all part of the networks we want to explain" (Latour 1988b). (In passing, we should also note how Latour, intentionally or not, is also using the very concept he wishes to escape, namely „explain"). The reason why he seeks to escape these disciplines has also been mentioned: He wants, by all means available, to escape not simply the modes of understanding that he describes, but also the institutions, the networks within which explanations thrive and grow: „Do we wish to offer more powerful explanations, that is, to transfer power relations from the setting studied to the centre of calculation studying them? Do we lust for power and recognition?" (*ibid*.). If that is Latour's intention, retrospectively we must deem his project to have been a failure, exactly because of its very success. In Paris alone, a number of universities are doing courses in Actor Network Theory, and it's network has indeed been spreading worldwide (Fuller 2000).

So much for preconditions and prejudice: even more than most, Latour cannot escape them, and I will not take more time to dwell on that part of his strategy. But we should ask: can we understand scientist without resorting to any of the language deployed by them? Will we be corrupted if we try and understand some of their intentions and something of what makes them tick? It is understandable if Latour, in fighting the hegemony of the natural sciences, goes out of his way to establish alternative ways of understanding science and society. But surely science already makes up central parts of our socialisation and surely it cannot be that bad to try and understand some of the concepts by which scientists work and by which they also understand their own work? And surely, taking into account the views of others from time to time must indeed grant a higher degree of *symmetry* than does imposing the construct of field ontology onto practicing agents.

Excluding scientists from the description of science may end up distorting central disciplinary issues involved in the production and distribution of knowledge. We have seen how Latour, first and foremost in *Laboratory Life* sought out the point of co-production of nature and society, and how he had to enter the actual site of that co-production, the laboratory, in order to get to that point. And, later, in following a scientific fact through society, he expands this perspective (Latour 1987). However: for most practical purposes, particularly in the politics of science, facts and artefacts do not represent themselves. They are represented by scientists. Scientists deploy ideas and methodologies in their negotiations with the material, and they also deploy many of the same ideas and methodologies in representing facts of nature to the wider society. We may miss out on important aspects of the production and distribution of knowledge if we do not take this into account.

Two sligthly different strategies of contextualisation are those entailed by micro-sociological or ethnographical methodologies. Philosophically and historically, these positions may be connected to authors like the late Wittgenstein, Clifford Geertz, Alfred Schutz and Harold Garfinkel. In difference to the latourean strategy of field ontology the approaches of Andrew Pickering (1995) or Karin Knorr Cetina (1999) may be seen as more amenable to hermeneutic analyses, as the conception of action and intentionality is emphasised stronger by these authors. In a way similar to Latour, Pickering and Knorr Cetina understand their own theoretical enterprises as distinct from traditional sociological or anthropological anayses, insofar as material agency is ascribed a far more central role in the creation of knowledge. Hence the conception of „posthumanism“ (Pickering). Whereas Pickering will talk of „the mangle“ or the „dance of agency“ in describing the emergence of new constellations of knowledge (Pickering 1995), Knorr Cetina deploys the conception of „Wissensmaschinerien“ for the hybridised construction of knowledge. And so the main analytical problem becomes one of describing the knowledge processes thereby entailed.

First of all, we should note how both of these authors aim to overcome what they (and many others) see as a decisive shortcoming in Latour's conceptual apparatus. This is the already mentioned fact that Latour does not allow for genuine descriptions of (scientific) intentionality, although he cannot but presuppose intentionality when seeking to understand the actions of others. This move becomes even more absurd as he occasionally seems to find few problems with ascribing something close to intentionality to *non-humans*, as for instance scallops (Callon and Latour 1992). Hence, Pickering writes that

„I want to discuss an aspect in which symmetry between human and material agency appears to break down. I want to talk about *intentionality* –a term I use in an everyday sense to point to the fact that scientific practice is typically organized around *specific plans and goals*. I find that I cannot make sense of the studies that follow without reference to the intentions of scientists, to their goals and plans, though I do not find it necessary to have insight into the intentions of things“ (Pickering 1995:17).

Similar to Latour, Pickering also shuns explanations, be they taken from the natural or the social sciences. Also for him, „description must take their place“. The fear of copying the explanatory frameworks of natural scientists and sociologists, and thereby reduce the fullness, the real-time happening of the context, leads him to look for emergent patterns in the interplay between agents (scientists) and matter, patterns that cannot be explained or predicted, but that can nevertheless be *understood*:

„This is my basic sense of emergence, a sense of brute chance, happening in time – and it is offensive to some deeply ingrained patterns of thought. The latter look for explanations – and the closer to the causal, mechanical explanations of physics the better – while it seems to me that in the analysis of real-time practice, in certain respects at least, none can be given. I can do nothing about this, but it is best to be clear about it from the start. The world of the mangle [i.e. the interplay between matter and intentionality] lacks the comforting causality of traditional physics or engineering, or of sociology for that matter, with its traditional repertoire of enduring causes (interests) and constraints. I must add, though, that in my analysis brute contingency is constitutively interwoven into *a pattern that we can grasp* and understand, and which, as far as I am concerned, does explain what is going on“ (Pickering 1995:24).

Here, explanation is subordinated to micro-sociological understanding. Also for Pickering it is important to demarcate his own enterprise clearly from that which he describes (the building of the bubble chamber in experimental particle physics, the search for the quark and so on). However, for the purposes of the following analysis, I should like to make the following remark: Pickering allows for the „plans and goals of scientists“, i.e. their intentions, to be part of the description. He does not, however, seem to be very much interested in those institutional plans and goals that also go to constitute scientific activity, as for instance, funding, the drive for patentable and marketable products, or political incitaments to undertak certain kinds of research and not others. I do not really intend this as a *critique* of Pickering, but I do wish to point out that there are few reasons why we should not expand the micro-sociological scope to include other plans and goals[20]. In the end, one main goal of STS is to

[20] In a later work (Pickering 2005) Pickering *does* indeed expand the scope of the analysis to include macro-sociological modes of explanation. I refer to the above work of Pickering as an important instance of what I take as a wide-spread tendency; it is not necessarily as a strong critique of Pickering the author. However, also in that

describe science as a social institution. I see few reasons why we should restrict that undertaking to the activities and intentions of scientists only. Obviously, this hinges on what one wishes one's analysis to show. Focusing on more of the „external" issues of science will inevitably also lead to less detailed descriptions of what goes on in the laboratory.

Another example of the micro-sociological shortcomings are found in Knorr Cetinas *Wissenskulturen* (1999/2002)[21], in which the author undertakes a comparative study of two different „cultures of knowledge": that of high energy physics (CERN) and that of molecular biology. Let me give some examples of how the normative dimensions of science are described (or rather ommitted) in this book.

First, as to one of the main goals of the book, described in the introduction. Here, Knorr Cetina states that:

„Die Betrachtung der epistemischen Maschinerien der Wissenserzeugung zeigt for allem eines auf: die Fragmentierung zeitgenössischer Wissensprozesse. Sie bringt die unterschiedliche Architektur empirischer Ansätze, die spezifischen Konstruktionen des Objektbereichs, die speziellen Ontologien technischer Instrumente und die verschiedenen sozialen Formen zum Vorschein, die in verschiedenen Wissensgebieten relevant sind. Anders ausgedrückt, sie weist die Existenz verschiedenartigster Wissenskulturen nach, und dies wiederum stellt die these von der Einheit der Wissenschaft infrage. Es widerspricht der mit dem Wiener Kreis der philosophie verbundene Annahme, dass es nur *eine* wissenschaftliche Methode, *eine* Art des Wissens und nur *eine* Wissenschaft gibt" (Knorr Cetina 2002:13).

This is about as far as the normative commitment seems to go, and with respect to laboratory studies this perspective does not seem to have changed all that much since Knorr Cetina and others introduced it more than twenty years ago. When posed in this manner, there are no questions that cannot be answered by *description*, by demonstrating the manifoldness and complexity of even one single discipline, like that of high energy physics. In one section Knorr Cetina remarks upon the impact of of the human genome project on the research practices of molecular biology. The HGP, it is stated, will probably lead to processes of „Routinisierung und Standardisierung" of research (*ibid*., 126). Being as it is one of the first lessons of laboratory studies that the laboratory effectively transforms the natural and social environment (*ibid*., 45), one could expect and hope for something more of a comment on the

later work Pickering remains committed to the description of emerging patterns. Insofar as normative conclusions are drawn, these are treated as internal sociological questions rather than questions relating to the wider field within which the sociology of knowledge operates.

[21] I quote the German edition which was published three years after the English edition.

subject from one of the pioneers in the field, but the analysis remains on the level of observation.

One science that entails the full potential of transforming society once and for all, is high energy physics, the other experimental science described in the book. But the imminent dangers of the research are not mentioned. Neither are the exeptional scales, in terms of resources, scientists, engineers and technical equipment, that the discipline requires offered much critical reflection. Recalling the Heideggarian analysis of technology, it seems that the two sciences described in *Wissenskulturen* are emminent examples of experimentation put to the service of technological imperatives, in which ever more resources, natural and social, are at stake. On a very basic level, these are normative issues. But such generalisations presumably run counter to the pluralistic and descriptive methodological strategies entailed by Knorr Cetinas analyses.

One reason for such strategies as the one mentioned above may go as follows: there exists, by many STSers, a distrust of generalisations frequently connected to a long-prevailing image of science: "The Baconian image of the man-made scientist interfering with the woman-nature …projected on to nature itself…central causal structures that dominated everything that happened" (Hacking 1988). This would be parallel to Latour's distrust in explanations. As put by one author, the "unsplendid isolation of STS" may "in fact be a self-imposed exile from the terms and assumptions that inform the discourse of mainstream theorizing" (Bogen 1996).

I have argued that proponents of contextualist knowledge in science studies, for all the importance and timeliness of their work (I most certainly want to emphasise this), often end up giving somewhat one-dimensional descriptions of contextuality. While keeping many of the valuable insights from STS, i would like to emphasise the importance of relating to disciplines that may be conceived as „too traditional" by practitioners of these „disciplines", significantly political theory. For the sake of this project this will be illustrated by the connection to *bioethics* carried out in a later chapter on autonomy. For now, let me just say something more about contextuality.

The theoretical perspectives described above may be termed one-dimensional contextualisations, insofar as they seem to impose themselves on the agents (scientists) in ways that may render the descriptions given somehow decapitated, especially when it comes

to the normative implications of social studies of science. In the case of Latour, the actors are not really allowed to speak for themselves as he imposes his field ontology upon them. In *The Pasteurization of France,* for instance, Pasteur comes out as little more than a strategically clever power politician (which he may very well have been, but he most certainly must have been more as well). The analysis is certainly interesting and provocative, but it is far from communicative.

In the case of Pickering and Knorr Cetina, the problem may easily become the opposite: although their projects may very well be carried out with a critical intent, this intent is never allowed to express itself because of the very fullness of the context: the *mangle* and the *Wissensmaschinereien* seem to be perfectly self-sufficient (perhaps also self-referential), and few or no external voices are let into the experimental setting[22]. We end up with the perspective of the scientist *or* the ethnomethodologist. Either, the ethnomethodologist accepts the epistemic authority of the scientist, or she denies it. In the last case, the sole frame of reference becomes that of ethnomethodology, and it is little wonder if the scientist remains incomprehensive, or even hostile. In the opinion of a reflected scientist, expressing himself about Knorr cetina's analysis of high energy physics:

„One reason for the controversy between science studies and scientists may be linked to the distinction between natural and social science as „hard" and „soft" science respectively. Though the validity of this distinction may be questioned (a strong social constructivist would probably deny it due to the claim that all science is social), it is difficult to avoid since natural scientists from the very beginning of their careers are thaught that what they deal with is most of the time brute facts. If, on the other hand, a career in social science implies professors and books which have a variety of ways of looking at the same subject, cultural clashes such as „Science Wars" are to be expected" (Zinkernagel 1996).

…evaluating

But surely, human experience consists of more than what can be offered by these two opposing perspectives only. For instance, we are all socialised into some kind of understanding of what constitutes a democratic institution. Coming from more or less the same cultures (not epistemic cultures), we are also able to share in and understand visions of the good life and constitutive values, even though we may not agree on the character of these or which implications to draw from them. Furthermore, we are capable of making *qualitative* valuations of their immanent values and goals. To put it with Tranøy: These valuations are highly likely to be related to "external" values, as for instance that of openness and

[22] The term "critical" should also be taken to imply "self-critical" in a sense similar to the Kantian conception of critique.

transparency as both a democratic and a scientific value (Popper 1957; Feyerabend 1978; Fuller 2003). When put in this manner it becomes clear that it is *not* simply a matter of who supplies the most adequate account of scientific and experimental practice, the scientist or the epistemological realist with his explanations, or the social scientists with her description. It is also very much a matter of the social and environmental functions and consequences of the (natural) sciences and of technology, and of their relation to some evaluative standards supplied by us as citizens and scientists (in that order).

This then, would point towards a normatively informed debate drawing on a wide range of arguments and perspectives in which the question of realism, so central to the science wars, is highly subordinate to *practical* concerns traditionally addressed by social philosophy and political science. Although the practical and performative dimensions of science have been underlined for years by STS (Pickering 1992) these concerns have not been adequately articulated. This is a central concern within a recent and promising turn within STS itself, the emerging idiom of *co-production* of scientific and social order, in which the normative underpinnings of science and technology studies as well as their relation to political science in the more traditional sense of the word is emphasised rather than suppressed (Jasanoff 2004).

As shown by the quote from Zinkernagel: when the contextuality of scientific knowledge is adressed in the above described manner we risk ending up with incompatible perspectives in which we may never get any further than to state which is the best way of relating to the world: should we aim simply to describe it or should we aim to explain it? There seems to be little middle ground and few points of reference for communication from which to get started. At this stage we are getting close to Steve Fuller's critique of science studies: as good followers of Thomas Kuhn many STSers seem to have accepted his thesis of incommensurability, stating that different disciplines or paradigms cannot meaningfully be compared as regards their value or their usefulness. Each paradigm to itself, each discipline and each paradigm is auto-referential and so external questions have little meaning and bearing on questions of methodology:

"…the inquirer's politics is largely a personal matter that lies outside the proper modes of STS inquiry. STS practitioners are forced to reflect *methodologically* on their status as political agents only once they are thrown into situations that require them to defend the integrity of their research" (Fuller 2000:358).

In order to escape the dilemma of which perspective should be preferred, the explanative ideal of science or the descriptions offered by social scientists, we may have to make reference to such ("external") values as for instance that of democratic openness. First and foremost, making reference to some value that is not the exclusive domain of either of the two disciplines renders the whole affair more open. This is to say that disciplines also contain some normative dimensions bearing on argumentative *weight*, not relying upon descriptive accuracy alone. Disciplines also rely upon important decisions about which aspects of reality should be studied and which should be excluded. One main contention of both social scientists and philosophers has been that neither science nor technology is value-free or neutral, as is often implied in dominant accounts. However, if we do not also recognise the fundamental normativity of our own undertaking as social scientists, we may simply end up reifying this old image.

According to the philosophy of Charles Taylor this implies that we also allow for what he terms *strong evaluations* into the conceptual and methodological framework with which we approach science as a social institution (Taylor 1985b). Without pertaining to give a full analysis: Strong evaluations imply the reference to fundamental values as basis of choice between alternatives for action, and that the reference to such fundamental values is taken to imply some fundamental difference concerning qualitative worth: "strong evaluation is concerned with the qualitative *worth* of different desires" (*ibid*.), 16. As such, it may even imply the use of words like "good", "base", "righteous", "undemocratic" and the like.

Taylor's conception is best understood with reference to its counterpart, *weak evaluation*. Weak evaluations are typically given through utilitarian calculus in which the main frame of evaluation is the desirability of this or that outcome: Will I enjoy my dinner more if I have the fish than if I take the meat? If I fly with KLM I get to Barcelona faster; if I chose Air Berlin it will take more time but it will be cheaper. Which company should I chose? In these cases, one desire will in the end override the other and the choice will be made. I switch from the one to the other quite easily, and in the end the case may be settled by a straightforward calculation (indeed the main precept of utilitarianism). Not so in strong evaluations. This is not as simple as to state that strong evaluation is qualitative whereas weak evaluations are quantitative. A strong evaluation can never be given in "value neutral" terms, and many weak evaluations bear on the making of qualitative distinctions, such as that between fish and meat. The main difference, as already indicated, consists in the reference to some value (allegedly)

fundamental to human identity and activity, and it will typically be expressed by reference to strongly value-laden terms. Furthermore, a strong evaluation may decide between alternative weak evaluations, but this does not work the other way round. A strong evaluation can only be changed for another strong evaluation which is, in the end, judged to carry more weight:

> "…when in weak evaluation one desired alternative is set aside, it is only on the grounds of its contingent incompatibility with a more desired alternative. But with strong evaluation this is not necessarily the case. Some desired consummation may be eschewed not because it is incompatible with another, or if because of incompatibility this will not be contingent. Thus I refrain from doing some cowardly act, although very tempted to do so, but this is not because this act at this moment would make some other desired act impossible, as lunching now would make swimming impossible, but rather because it is base" (*ibid*., 18-19).

Now that we have become this much wiser, let us return to the issue at hand. If we accept strong evaluations as part of the context from the very outset, this will also have its bearings on our methodological choices. First and foremost, the question of who is "right" will not simply bear on the question of who gives the best account of scientific practice, the scientist himself or the social scientist, but may also be brought to bear on the wider issues of the goals of science, and also on its applications and its consequences. Indeed, this would be the full implication of the performative idiom in science studies (Nowotny, Scott et al. 2001; Jasanoff 2004), or of the practical turn in social philosophy (Taylor 1971-1972; Habermas 1981). As forcefully argued by these philosophers this entails the giving of *substantial* reasons (Habermas), or on the *articulation* of strong evaluations (Taylor). Within such a conception of theoretical activity there is no absolute shelter, be it ethno-methodological or "field-ontological"; reference has to be made to a wider range of sources. This is of course not to state that every description of scientific practice is supposed to imply some strong evaluation, which would indeed contain overcharging the context again, this time with what Hegel termed the moralistic world view. We are looking for decisive events and breaking-points in which significant decisions are made about the production and distribution of knowledge, and, where pertinent, we evaluate these according to what we take to be wider social interests. This also entails a specific kind of *work*, in which important issues are attempted transported out of more or less closed-off contexts and into a wider public and academic domain. Again, I would like to emphasise that this is what many STSers have been doing all the time. However, I also argued that these issues have not been reflected in the methods deployed in a satisfactory manner, and that this has something to do with notions of contextuality, of action and of agency.

If we accept these modifications of the contextualisation of knowledge practices we may still, as does Latour, speak of an "infralanguage" (Latour 1987; Latour 1988b), a language capable of travelling between contexts rather than operate from a perspective wholly external to the scientific practices. We must, however, accept: 1) intentionality as part of the practices as well as *material* agency (Pickering 1995), a point not reflected in Habermas or Taylor, and 2) that our infralanguage may also contain *qualitative distinctions* based on strong evaluations (Taylor 1985b) of the intrinsic values, goals, applications and consequences of scientific practice (Nowotny, Scott et al. 2001). Hence the notion of "reflexive hermeneutics".

I will now proceed by starting to sketch out how this expanded and hermeneutic view of "the context" may look when applied to science as a social institution. For the purposes of the following historical analysis the above remarks will entail the following: first and forermost the mode of analysis will be *reconstructive*, and it will not aim to give accurate, real-time analyses of experimental work or of the emergence (Pickering) of the institutional reconfigurations entailed by the experimental work. Compared to the descriptions of the microsociologists, the hermeneutic reconstruction may even be seen to *impose* logics to the historical happening that may not be accepted by the descriptive approach. Such impositions will have to be justified by reference to both descriptive accuracy and the normative concerns that informed our analysis in the first place. What may be gained is a perspective that does, after all, remain close to action and historical development, *and* which can be coupled to a more abstract perspective identifying specific sources and modes of acting and knowing that can be coupled more or less direct to the modern project. Relating to Beck, these are what he terms basic presuppositions of modernity (Beck and Bonss 2001). Relating to hermeneutics it is the *qualitative* understanding of specific modes of knowledge and of its organisation. In particular, hermeneutics adresses different modes of relating to the world, among which the ability to make strong evaluatiuon (Taylor) and give substantial reason (Habermas) are important assets. The point is, as already stated, to identify certain „breaking points" in which questions of greater concern so to speak announce themselves from within the situation, as breifly alluded to in the Heidegger chapter as „meanings arising within meanings". To give a central example from the following historical analysis: the articulation of the central dogma (Crick 1958), in which gene action comes to be perceived in terms of transfer of information is one such significant event.

The chapter on autonomy and bioethics is one good place for broaching these more substantial questions, and so I have placed it towards the end of the book. The chapter on genetics and on patentability should also be regarded as identifications of some of the central issues involved, whereas in the autonomy chapter I introduce more „strong evaluation“ perspectives and try to adress the wider context into which genetics and genomic medicine enters.

But before we can get to those issues, an interpretive framework has to be elaborated that tries to take into account the discussion so far.

3. An interpretive framework

During the course of the last two chapters I have consulted a number of theoretical positions. It has been stated that the general approach of the project is hermeneutic, and I have sketched elements of Heidegger's philosophy of Being-in-the-World and his later philosophy of technology. Through recourse to Habermas, Heidegger was criticised for an anti-social and indeed sociologically naïve position. The main problem, we may state with Habermas, is the total absence of making communication a subject, or, perhaps more accurately, of making barriers to communication *a practical problem to be solved*. As it is, communication turns out to be an essential part of both the problems of late modernity and to the articulation of possible solutions.

The above opposition between Habermas and Heidegger may indeed be taken to indicate the scope of "hermeneutics". Hermeneutics are not to be restricted to the Heideggerian framework, but must include a wider set of authors, like Habermas, Gadamer or Charles Taylor. I will use the Heideggerian analyses of Being-in-the-World and of technology, but it is indeed important to remain open also to those other authors, as they have recognised the importance and the necessity of making *communication* a subject of investigation. The question is *how* to embed communication. It emerges that it has to be embedded within structures of action.

I then went on to criticise the methodological dualism of hermeneutics after Heidegger. Whereas Heidegger may have been largely ignorant of the communicative dimension, he was not unaware of the *material basis* of human existence and its significance for the organisation of social action. As this dimension has been by and large ignored by hermeneutics, as well as by the humanities and social sciences at large, I went on to point to the general soundness of the approach taken by science and technology studies during the last thirty years or so. However, science and technology studies have a certain tendency towards some of the problems noted in Heidegger, in the sense that the normative dimensions of the own undertaking often go unrecognised. This may turn out negative for the sake of the central issue at stake, namely that of projecting strategies of action and communication for the future.

I now continue by sketching a framework of my own that *attempts* to overcome some of the above problems.

Transforming Heidegger's philosophy of technology

Two concepts of Heidegger's are of central importance: *Bestand*, signifying the stored-up potential of technology, and *Gestell*, the intellectual framework through which that storing up becomes possible.

Bestand signifies material agency as captured by modern technology. That mode of storing up which we call technology is rooted in some general capacity of nature and in our capacity for transforming and refining nature through intervention: nature has the propensity of being refined and of being stored up. A simple example that should also go well with the Heideggerian outlook on the world is that of chopping and storing wood for the winter. By cutting trees and making wood, we store up heat. The stock of wood makes for a primitive version of *Bestand*.

But modern technology proper takes more than the physical refinement of natural resources to come about; it also takes the mediation of intellectual analysis, of quantification and explanation. This comes about through the framework of *Gestell*, originally served to us by mathematics and physics.

However, Heidegger does not serve many clues as to how *Bestand* actually comes about through the intellectual medium of *Gestell*. Also here there is something to be learned from science and technology studies insofar as they direct the focus towards the actual experimental activity necessary for establishing technology. Ian Hacking (a philosopher) has also served important clues: intellectual *representation*, which may be termed a subgroup of *Gestell*, comes about as a result of material *intervention* achieved through experimental activity. This points us towards the material, technological and institutional configurations that make up the experimental contexts of scientists.

Because this project aims for a mid-range perspective rather than a micro-sociological or ethnographic perspective, as found in many science and technology writers, the central emphasis is not upon the many experimental strategies and complexities that go to constitute the scientific object, but rather upon the drive towards establishing and stabilising the techno-medical object as a socially powerful agent. Although experimental activity may be portrayed as almost infinitely complex and heterogeneous, I take it that one central and immanent

concern of most experimental activity is that of achieving standardised technological products (objects) capable of serving some wider social need, in this case that of promoting health.

Hence, I wish to point towards the organisational capacities of the techno-medical object, and its potential for organising action on a broad scale and across distances of time and space. One central feature of the techno-medical object is its capacity for storing up material agency and to render agency transportable across time and space. This is only possible through isolation, refinement and standardisation of highly specific aspects of nature. Experimental activity aims for reproducible results, which, when repeated on a sufficiently broad basis, legitimates and makes possible the manufacturing of the techno-medical object. It is this that can be transported to other contexts and administered, also this in more or less standardised ways, to fulfil some practical purpose, like making a diagnosis or, even more powerful, to serve as a therapy. I will return to this in more detail below, where I will focus upon the different kinds of action facilitated through the techno-medical object.

As briefly described, the technological object comes about as a result of intervention with the material, and it is aimed at refining and storing up material agency. Experimental activity, for all its complexities, has as one of its main purposes such storing up through standardised and repeatable action. Such action is only possible within an institutional setting that has been constructed to promote experimental intervention. Experimental apparatuses and materials, like Petri dishes and different reagents, and technological equipment, for instance mass spectrometers or computers, are situated within institutional settings designed to serve the purposes of experimentation: the laboratory. In the biomedical context, the main justification of the laboratory, we may state, is its close connection to *the clinic* (Bernard 1957). The techno-medical object finds its main application and legitimacy through its effective application to the clinical context, the main purpose of which is to promote health and human well-being.

All along the way from experimental intervention to clinical application, the object is accompanied by some intellectual and linguistic *representations* of its workings, of the mechanisms guiding material agency. This representation has so far been described in terms of the Heideggerian conception of *Gestell.* However, in Heidegger, *Gestell* seems to be understood in some semi-mystical sense, in terms of epochal being or the like (Kolb 1992).

I now want to recast the Heideggerian conception of *Gestell* in more communicative and sociological terms. It must then be recognised that the proper representation of nature's workings cannot be conceived of in terms of some historic entity that imposes itself on the (more or less) unknowing actors, but rather something that is constructed and negotiated within complex networks of social meaning and material agency. Experimental activity, to start at the beginning, is a matter of negotiating possible pathways with the material, but it is also a matter of negotiating social relations, and indeed the two cannot be wholly separated without losing sight of important issues involved. Furthermore, experimental activity is not carried out in isolation, it is a communal endeavour. In order to establish experimental relations and to refine material agency, a whole set of issues has to be agreed upon and established in advance: which materials and organisms to use, fundamental concepts and methodological framework, experimental outfit and design, how to organise work in the laboratory and so on.

For these purposes, the medium of *theory* cannot be disregarded. Theory is organised representation of material agency, embedded within a complex field of experimental apparatuses and experimental institutions, which again makes up the central sites of the scientific community. In order to maintain the Heideggerian notion of technology as *Bestand*, we go by Hacking's notions of representation and intervening as basically two sides of the same coin: we cannot have the one without the other. In order to focus on social action aimed at producing techno-medical objects, however, we have to further transform the notion of representation. In Hacking's view, the notion of scientific realism boils down to the following statement: "if you can spray it, it is real"(Hacking 1983). Clearly, as the purpose of the techno-medical object is only fulfilled in the *clinical* context, Hacking's statement, although pointing in the right direction, is not totally satisfactory. In the end, the techno-medical object proves its reality through its capacity for organising *therapeutic or diagnostic intervention* in the life-world of the patient. This notion, I take it, also captures some of the basic insights of Heidegger: the techno-medical object gains its importance for our Being-in-the-World through its capacity for storing up material agency, which can then be transported and released at will in order to fulfil some practical purpose (by merging with human agenct). Hence, the techno-medical object is real if it serves the purpose of promoting therapy or diagnosis.

The counterfactual organiser (I)

I now introduce a concept of my own in order to: (1) keep the Heideggerian notion of *Bestand* (2) keep Hacking's insight about the practical, contextual and instrumental character of representing that agency through intervention, and (3) adapting these insights to the context of the life-sciences. The techno-medical object is, I take it, is represented through what I will call the "counterfactual organiser". As will be seen, counterfactual organisers that do not correspond "directly" to objects but "only" to the organisation of action as such are also to be found. These are legal, political or ethical principles rather than scientific principles. However, they are not to be regarded as absolutely separate: their reliance upon "scientific facts" is, in many cases, what establishes them as specifically modern categories of thought and action. And if categories of ethics, law or politics in many cases come to rely upon scientific representations of reality, they may just as often influence science or technology to move in desired directions, for instance by strengthening the professional monopolies of professional groups set to define, refine and operate "nature" within the modern differentiation of work, or by promoting research along specific pathways, for instance strengthening the search for powerful techno-medical objects. Hence, the social contract is not to be sought out along a symmetrical axis of consenting citizens only; it is also a matter of institutionalising nature. I will return to these issues. For now, I continue to follow the concept of the counterfactual organiser in its specifically scientific and experimental form.

The conception of "the organiser" as a scientific concept was introduced in the 1930s in order to explain embryonic development. Its general signification was that of "…a specific embryonic tissue which upon transplantation could trigger the development of a whole biological system"(Abir-Am 1982). In appropriating the concept for my own purposes, I take it to mean an intellectual representation of nature's workings that has come to be agreed upon by a wider community of researchers and which, although standardised, may take on a different meaning when transferred to a different context.

Importantly, the representation in question is termed an organiser because of its capacity for organising social action: it is an agreed-upon hypothetical framework that serves to direct and make possible inter-subjective action and communication in communities of researchers or clinical practitioners. As such, the organiser is a communal decision about nature.

In the language of the philosophy of science, it may be more likened to that of Kuhn's paradigms than to the hypotheses of Popper, but it is to be given a broader significance than both that does not differentiate sharply between science and non-science. This is important, because the main significance of the organiser resides in its capacity for organising social action, and thereby also of establishing social metaphysics. It is capable of defining the outlook on nature on a broad social basis. In genealogical (but not Foucauldian) terms, we may for the moment stick to the somehow simplified notion that the organiser, although not necessarily arising in the laboratory, gains its fundamental momentum through experimental action. It organises experimental action, but it is also rendered transportable to other contexts through standardisation: it makes possible standardised action also in other contexts than the experimental.

Central examples to be deployed in this project are those of the *specific action* of micro-organisms: the *specificity* of the antibody-antigen interaction and *the central dogma of molecular biology*. The central dogma, it may be stated, constitutes the scientific counterpart of present-day "gene talk" (Fox Keller 2000), and it makes up a necessary, though not sufficient condition for the strong social status that the gene has come to occupy. Centrally, the organiser operates on the interfaces between the experimental context, the clinical context and the life-world of the patient. Through its capacity for capturing material agency, it also achieves a strong social status. One early example of the organiser and its capacity for transforming social action was that of the *lesion*, established in the Paris clinics following the French revolution (Foucault 1973).

Next, the organiser has something to do with *causality*. Indeed, the organiser, in its original environment, was introduced in order to account for "the causal dynamics of embryonic development" (Fox Keller 1995:6). This is where the concept of the counterfactual enters: Propositions about agency, mechanism or causality are *contrary to facts*, in the sense that they guide our thinking about the general workings of the world, the things and the people in it. Hence, they are action-guiding principles established through the hypothetic pronouncement of relations among entities, what Kant termed *regulatory* ideas. Regulatory ideas are necessary for structuring experience into a coherent whole, but they cannot be definitely proven. Counterfactuals do not contradict facts. Quite the contrary: they serve to structure facts into meaningful and coherent events. It is the anticipation of some effect occurring through the nature of things, the outcome and consequence of some *agency*. Agency, in this

context, may be both material and intentional, or it may be restricted mainly to one of those poles.

In its most basic form, the counterfactual is a natural constituent of everyday behaviour. It is based in our everyday interactions with the world, the things and the other people in it, as carried out through ordinary bodily competences. It is the expectation or projection of the normal course of things to continue to move and function in the accustomed way (Hume 1978). For instance, if I drop this glass, I know that it will fall and that it will probably break. The breaking of the glass, in the everyday sense of the word, is caused by my opening my hand and letting it fall. It is the carrying-out of action *as if* its normal course (learned through habit) will also prevail in the future. If I lock the door, the persons on the outside won't be able to open it because of my intervention with the previous state of the door, and so on. If eleven persons go on a picnic together, nine of them eat the chicken salad, two do not, and then the nine persons that had the salad become ill, we infer that the illness was caused by the salad. This last case, it should be noted, is no longer as straightforward as those with the glass and the door; the latter case involves the knowledge that bad food causes illness. In this case, some scientific knowledge has inserted itself into our everyday reasoning (King 1981).

Hence, the counterfactual is also different from the mere observation and correlation of phenomena. To take an early example: the medical teachings of Hippocrates mainly based themselves upon a descriptive gathering and correlation of facts that often or normally occur together. But the descriptive facts were not connected and organised internally through theory. Whereas Hippocrates would state that "A and B normally occur together", modern science typically seeks to establish the stronger relation of "A caused B" (King 1981:195). The following quote from one early philosophical proponent of scientific biology, Ernst Mach, may illustrate the point:

> "Not all our ideas representing facts have the same constancy. Whenever we have a special interest in the representation of facts, we endeavour to support and corroborate ideas of lesser constancy by ideas of greater constancy, or to replace them by the latter. Thus Newton conceived the planets as projectiles, although Kepler's laws were already well known, the tides as attracted by the moon, although the facts of their movement had been long ascertained. We believe we understand the suction of a pump, the flowing of a siphon, only as we add in thought the pressure of the air. Similarly we seek to conceive electrical, optical, and thermal processes as *mechanical* processes. This need to support weaker thoughts by stronger thoughts is also called the *need for causality*, and is the moving principle of all explanation in science" (Mach 1896:172).

This *need for causality* also makes itself remarked in other areas of action organisation. As will be seen, abstract principles of agency, in this project represented through autonomy and patentability, are also outcomes of the *need for abstract principles for action* that has been evolving along with the inner dynamics of modernity. When transferred into principles for action, counterfactuals typically issue in *as-if* propositions: we act as if the principle of physiological specificity is universally valid and equally applicable to all cases[23]. Sociologically, counterfactuals have played a significant role in the rationalisation and modernisation of society. In accordance with the above insertion of scientifically established *as-if* principles of rational action into the everyday character of counterfactuality, the need for abstraction and rational presuppositions for action has grown along with the transformation of society from *Gesellschaft* to *Gemeinschaft*. However, whereas counterfactuals during first modernity would issue in more or less reliable certainty for action, in second modernity, they typically issue in terms of *risk*:

"Der begriff des Risikos ist grundlegend für unsere moderne Kultur, weil wir häufig in der Form des "als-ob" denken. Auf fast allen Gebieten des individuellen und kollektiven Lebens mussen wir die Zukunft gestalten, obschon wir wissen, dass ein solcher Entwurf selbst dessen Ausführung verhindert" (Beck, Lash et al. 1996:15).

Turning to the biomedical sciences, very specific aspects of nature are singled out, isolated and manipulated experimentally in order to determine their mechanical, chemical or organic workings (Bernard 1957). The particular aspect of nature corresponds to some specific perspective on the side of the interrogating mind brought about through an objectifying attitude (Husserl 1960), or, more to the point, some intervention aimed at establishing objective knowledge (Hacking 1983). The purification of the mutual correlation between perspective and aspect is only rendered possible through the experimental isolation of causes, through intervention using some apparatus or other. In experimental science, there is no access to the things themselves other than through the manipulation of things by the use of experimental tools and technological equipment (Fjelland 1991).

A great number of theories have been set forth to account for the nature of causality in general (Mach 1896; Keynes 1921; Mill 1963-1991; Mackie 1965; Hume 1978), in the biomedical

[23] And, as will be argued: we do something similar when we presuppose the patient as a rational actor or the invisible hand of the market as rational bases of action.

sciences (Mach 1896; Bernard 1957; King 1981; Vineis 2000), in genetics (Rose 1997; Sober 2000; Vineis, Schulte et al. 2001) and in the law (Hart and Honoré 1959; Mill 1963-1991). Obviously, in other disciplines, like the human and social sciences, we find different accounts, for instance those given in (Collingwood 1956; von Wright 1971).

In hermeneutics, we may speak of causality in more or less rigid ways. But due to the historical embedding and character of human existence, hermeneutics can never be used to forward one universal notion of causality. Notions of causality arise within the different scientific disciplines, and are, qua universal theories, *mainly* restricted to the context in which they arise. This is not to deny them a wider validity. But we have to ask of them something more than theoretical universality pure and simple[24]. As stated above, we take as our principle of realism for the biomedical sciences that of functionality, be it therapeutic or diagnostic. There is little point in denying the (universal) workings of penicillin, even when administered by a person who does not even know exactly how it works. As will be seen, the antibody was also such an object whose reality could be defended on a broad social scale because of its undeniable *effect*, which could be theoretically justified under the counterfactual presupposition of the specificity of the antibody-antigen interaction (Silverstein 1989).

Hence, denying, almost by principle, the notion of universal causality, for instance as offered in the physics of the early 20th century, is very far from proclaiming a universal scepticism on behalf of science, or endorsing "irrationalism". Such allegations stem from misconceptions about rationality in general, and about causality in particular (Toulmin 2003). I have described some of these misconceptions in chapter 1 in dealing with the Cartesian versus the Aristotelian anthropologies and with the notion of nature following from the physics and mathematics of thinkers like Galilei, Descartes and Hobbes. Today we hear these misconceptions repeated in calls for a deterministic biology and socio-biology (Rose 1997).

In fact, from the perspectives of most actors involved in the wider administration of the biomedical sciences, it is the social and material reality of the counterfactuals, it is what they allow us to do, which establish them as reasonable platforms for action. Although theoretical

[24] Take mathematics as an example. Qua theory, mathematics is "universal" as long as restricted to its sphere of validity, i.e. mainly western societies or societies/cultures that recognise and understand the meaning of describing nature in mathematical terms. However, this universality remains empty and of scant authority as long as mathematics cannot also be applied for some specific purpose, for instance that of measuring the land or predicting the influence of the moon on the tides with greater accuracy than was *previously possible*.

and experimental mediation is clearly required, it is the possibilities granted to us within a social context, promoting health, which ultimately legitimates the interventions accommodated and made possible through counterfactual organisers.

Counterfactual organisers in the biomedical sciences allow for the communal task of scientific intervention with material reality, which may in the end result in the successful production of techno-medical objects. This amounts to stating that, fundamentally speaking, they are historical entities. This should not defer us from taking them seriously as epistemic statements, indeed as "the best account" (Taylor) of agency and causation within their proper disciplinary domain.

A hermeneutic of the techno-medical object

So much for the "counterfactual" and "the organiser" considered as separate concepts. However, when put together, they are meant to illustrate the following: By singling out and isolating very specific aspects of reality to be investigated, they simultaneously serve to organise both material reality as well as the scientific community itself. The fundamental site of the negotiations of new socio-material pathways is that of the laboratory, or, in Rheinberger's words, experimental systems (Rheinberger 1997). Although the conception of the counterfactual may direct our attention towards Popperian notions of science, such notions are to be avoided. According to Popper, science is a theory-driven undertaking in which the theoretician asks the fundamental questions and the experimenter performs the dirty work. But such conceptions of science are bound to lead us astray: "Every experimental scientist knows just how little a single experiment can prove or convince. To establish proof, an entire *system of experiments* and controls is needed, set up according to an assumption or style and performed by an expert", Ludwig Fleck, quoted from (Rheinberger 1997:27).

Rather than regarding counterfactuals as clearly stated hypotheses to be confirmed or falsified by experiment, they must primarily be regarded qua organisational principles embedded in communities and experimental systems. Rather than regard them as clearly stated propositions to be tested out, they should be seen as vague notions, not frequently invoked explicitly except from in basic textbooks and broad overviews of the field. As such, practitioners new to the field may need to revoke them qua basic theoretical presuppositions, but for the more skilled practitioner they will be second nature, internalised in the body through its many operations within the experimental system (Dreyfus and Dreyfus 1986). Thus, the

"falsification" of the counterfactual organiser would not come about as the result of carefully designed questions posed to the material, but rather through their lack of ability to organise experimental action. That is: gradually, material or social anomalies would turn up that asked for serious restructuring of the experimental system as well as the theoretical framework through which experimental action is guided. One example of such a restructuring that will be described is that of the separation of embryology and genetics up until the 1940s. For a long time, they shared work between them: genetics dealt with transmission of heredity, whereas embryology dealt with the development of the single organism. However, in the long run that separation provided more questions than answers: there had to be a connection between the two realms of physiological function (Fox Keller 2000). With the identification of DNA as the hereditary material a reconfiguration of the two disciplines, hence also of the experimental system, was inaugurated, and by the 1960s the new discipline of molecular biology had established itself. A fundamental asset of molecular biology's newly established authority was its alleged ability to bring the two aspects together within the fold of gene action.

Hence: Specifically closed-off compartments of physical reality correspond with scientific activity as embedded in different experimental systems, dealing with different aspects of reality through the cultivation of specific perspectives peculiar to the single disciplines. The authority of the scientific discipline depends in important ways upon its capacity for representing and intervening with, manipulating and controlling, those specific aspects of physical reality. For that purpose, scientists deploy specific perspectives as embedded in the use of this or that specific methodological or theoretical framework, in its turn situated within a specifically constructed experimental system.

In the (biomedical) sciences, counterfactual organisers are used in order to negotiate new relations with material reality in order to produce standing reserves. The standing reserve is deployed for some practical purpose, centrally that of curing disease. In so doing, we invest the technological product with agency and authority in matters social and medical. This investment could not come about other than through the intermediation of theoretical representation carried out in experimental action by the use of technological equipment. Through experimental action, the scientific community transform material and social reality. When successful, technological objects emerge that serve to facilitate and promote standardised ways of action for the purpose of promoting some social good. In this way, we delegate organisational authority to the techno-medical object.

If this analysis is accepted we may draw the following conclusion regarding the discussion of realism versus social constructivism: the scientific object is not represented through the signifier. It is represented by the scientific community. The community, furthermore, is situated within its institutions and its experimental systems. From this we may also draw a conclusion regarding the social and political legitimacy of scientific communities: legitimacy does not primarily depend upon the giving of correct representations of reality, but rather upon efficient manipulations of and control with reality. Somewhat simplified we may infer that the scientific community retains its legitimacy as long as it is capable of controlling and manipulating those aspects of reality that make up its specific domain of expertise.

I will now proceed to expand somewhat the hermeneutic of the techno-medical object. In a sense, the reconstruction offered is genealogical, insofar as it is designed to follow the object from its inception in the laboratory, continue through its administration in the clinical context, where it is finally embedded within the life-world of the single patient. I do not profess to offer any "thick descriptions" (Geertz) at this point. Rather, the description is analytical insofar as it proceeds from the notion of specific "proto-objects". The close intertwining of things (objects) and human agency has been emphasised from the very outset of this project. Hence, I continue by describing proto-actions through proto-objects: specific technological or scientific objects belong to some specific task to be performed at some stage of experimental or clinical work. Specific objects organise specific actions and vice versa. Perhaps the most clear-cut example of this will be the division between therapeutic and diagnostic objects as facilitating therapeutic and diagnostic action respectively. However, I start out by giving a short account of experimental action.

The laboratory

There is no right answer to the question: Which comes first, experiment, theory, invention technology, …? Ian Hacking, *Representing and intervening*

Most of the things that I wanted to say about the experimental context have already been stated above. The rest, and indeed the main part, of what remains to be said will be carried out in terms of historical reconstruction rather than theoretical analysis. I therefore confine myself to a brief recounting of some analytical tools offered by Rheinberger, namely that between *epistemic* and *technical* things.

"Epistemic things", says Rheinberger are "material entities or processes – physical structures, chemical reactions, biological functions – that constitute the objects of enquiry" (Rheinberger 1997:28). As objects of experiment they are by definition indeterminate entities, they are the counterparts of the questions posed through the experimental system, possibly also through the projection of the counterfactual organiser. The object 'in itself' is nothing but the object at a certain stage (beginning, transitory or end) of the research process in which the object, considered in *that* specific aspect, from *this* specific perspective, from which the object can be kept under control by the apparatus, conceptual, technological or instrumental, which forms its milieu. The apparatus in question may be a simulation of the natural milieu of the object, it may intervene or manipulate with the natural object, or it may produce a new object, not pre-existent in nature. This is of my articulation and not Rheinberger's. But the fact remains that epistemic things appear more in the shape of the question than that of the answer. They are by nature vague, as they "embody what one does not yet know. Scientific objects have the precarious status of being absent in their experimental presence; they are not simply hidden things to be brought to light through sophisticated manipulations", *ibid*. However, as the object emerges as a more strictly defined entity, it may to some degree be defined, -through "a list of its constitutive actions", Bruno Latour, quoted from (Rheinberger 1997:28). Hence, the epistemic object is primarily what it does. As the characteristics of the object are gradually exhausted (in a relative, never absolute, way) it mat turn into a "technical object". In that case, it has been sufficiently stabilised to serve as a tool for further research rather than to serve itself as the prime subject of research. In that way, the object becomes part of routine, it is "black-boxed". I take it that only when objects come into focus in the above sketched manner can they merge with and make up a constituent part of the experimental system as well as the theoretical framework therein embedded. Hence, as the object is stabilised it may fall into accordance also with the more general framework of an organising principle.

Technical objects serve the wider purpose of embedding researches into the unknown, i.e. investigations of epistemic things, within the experimental system. As such, they may be seen to reside in the space between experimental apparatus, models and model organisms, theoretical and methodological presuppositions and the epistemic object. One visually powerful example may be that of genetic and physical maps established through the hunts for single genes in the 1980s. Once established as more or less stable frameworks, these would in turn serve as important tools for the discovery of new genes, and, eventually they would also

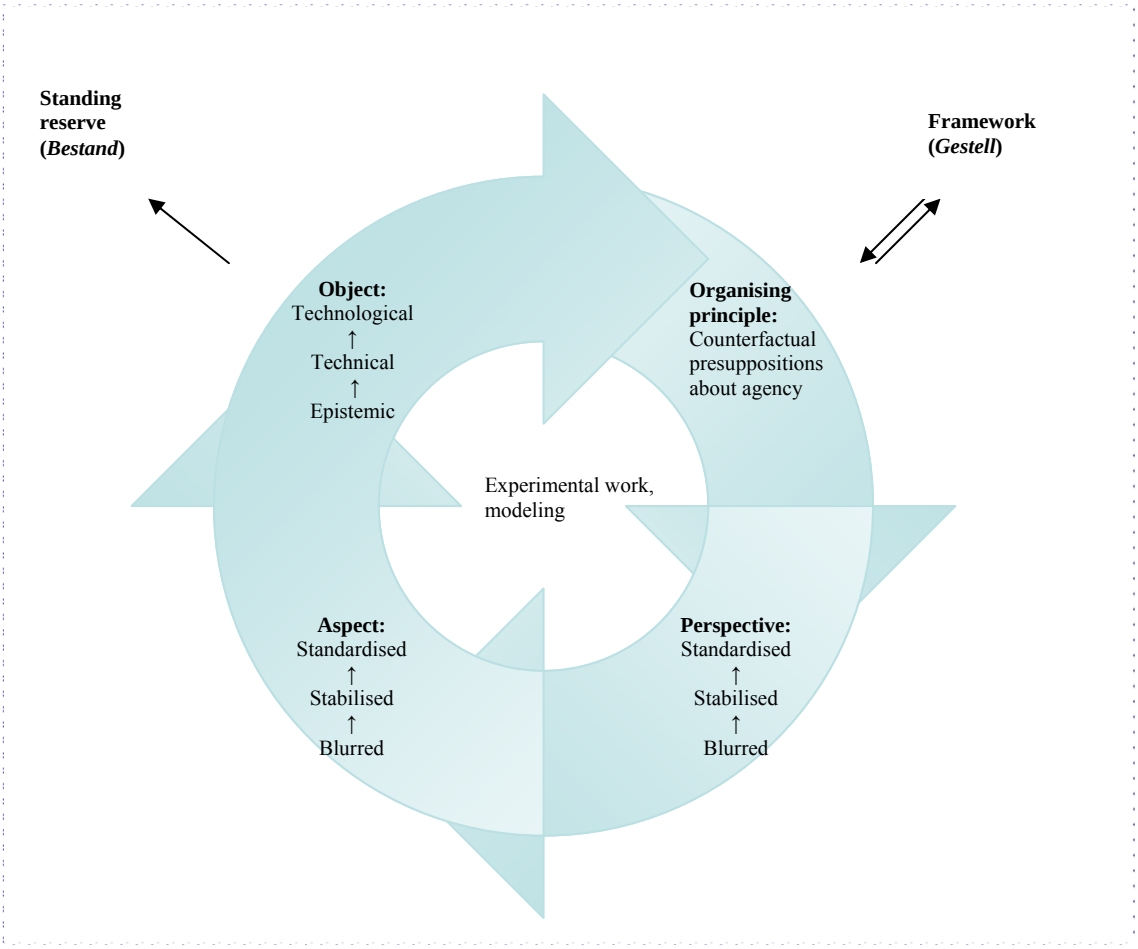
be used to "anchor" the sequencing of the genome itself within what was already known about chromosomal and genetic structures. This obtained, the new and improved sequence maps could in turn be deployed to correct the initially used genetic and physical maps. This should also contribute to highlighting the relative difference only, between epistemic and technical things. They are involved in reciprocal negotiations in which one influences the other, and so are not absolutely separable, other than for analytic purposes:

> "…within a particular experimental system both types of elements are engaged in a nontrivial interplay, intercalation, and interconversion, both in time and space. The technical conditions determine the realm of possible representations of an epistemic thing; and sufficiently stabilized epistemic things turn into the technical repertoire of the experimental arrangement" (Rheinberger 1997:29),.

In addition to epistemic and technical things we should include a further dimension: the object that has been sufficiently stabilised so as to leave the laboratory and enter a clinical or commercial context. To return to the Heideggerian conception of the standing reserve: technological objects are stabilised and standardised so as to store up material agency that can be released at will. In the context of this project, such objects are primarily therapeutic, but they may also take the character of being diagnostic or preventive. In these latter cases the control with material agency is weaker and has to rely upon different measures. I will have some more to say about this below.

Through the inclusion of technological objects we leave the experimental context as described by Rheinberger, and in so doing I would like to make a methodological and reflective note on that move specifically. Rheniberger's notions of epistemic and technical things clearly owe something of their existence to the philosophy of Heidegger (as interpreted through Derrida). In a short note on that relation, Rheinberger makes an interesting note on "technoscience" that is highly relevant to the undertaking of establishing an analytic of techno-medical objects. Rheinberger cautions against the Heideggerian tendency towards assimilating technology and science. In Heidegger's terms, science stands in the service of the technological imperative, and science will for that reason tend towards being enrolled by large-scale scientific projects with strong technological underpinnings.

A hermeneutic reconstruction of the experimental context



To a certain extent, we may state that the Human Genome Project partially serves to prove Heidegger's assumptions. Opposing that position, Rheinberger reiterates a point that has also been made earlier on in this project: "Let me claim, in contrast, that it is exactly the viewpoint of opposing philosophy to technoscience and identifying scientific knowledge with "technknowledge" that finally leads to the exile of the "theme" [Being] and to its surrender to Heideggerian "thinking" (Rheinberger 1997:31).

While clearly not wanting to subtract from this point, I would like to make an argument in favour of my "mid-range" perspective as opposed to Rheinberger's fundamentally "micro-range" perspective. The main point has already been mentioned: Within the biomedical sciences there is a strong drive towards establishing techno-medical objects that serve the wider goal of promoting health. As the social influence and importance of biomedical

research increases, this point becomes more and more evident. We may, therefore, legitimately focus on those specific aspects of biomedical research aimed at establishing useful objects, first and foremost for the clinical context. Already Claude Bernard stated this principle as one of the main legitimating forces of experimental medicine. We may legitimately speak about a technological *telos* inherent in the life sciences (obviously also as related to agriculture). This perspective tends to disappear in micro-scale analyses such as that of Rheinberger, which typically tend towards deconstructing any notion of determinism inherent in macro-scale analyses through close descriptions of the complexity of research. The same would be the case with the "open-ended" becoming or emergence of the social and material as described in (Pickering 1995; Pickering 2005).

That stated, however, the historical and sociological reconstructions carried out in the next part of this project agree with Rheinberger in the disapproval of Heidegger's deterministic view of technoscience. However: both Rheinberger and Heidegger have that in common that they, in their analytical frameworks, overlook other forces that may exert their influences on experimental work. Such forces/institutions may be that of clinical utility and that of the increasingly strong influence of the economy. Hence, if a specific *drive* towards closure of the open experimental context is not to be found within experimental work itself (Rheinberger, Pickering), then it may be found in other structuring factors (Bloor 2005; Harwood 2005).

Thus, I continue by expanding the scope of analysis drastically, first to the clinical context, then to the life-worlds and to regulatory bodies. However, in order to restrict the scope, I will remain, by and large within the conceptual frameworks of the counterfactual organiser and the techno-medical object.

Technology transfer

As the scientific enterprise expands, the object is socialised: it falls under the influence of different research communities, bodies of science policy as well as other action systems, as for instance economy and law. This means that the scientist may have to fight in order for his perspective to remain in correspondence with the relevant aspects of the object.

The (particular) scientific community remains in power as long as its object remains stable. As long as the scientist and his community is capable of giving an account of the object which corresponds to the actions which it is set to organise, and as long as they are capable of

controlling and manipulating the object for the purposes for which it is organised, the scientific object remains 'identical to itself'. Hence, it makes no difference that the object is changed by the progression of knowledge, and we do not need to presuppose an unchanging, geometrical or otherwise, universe, parallel to the perceived world, in which the object is finally made to correspond to its idea. The object remains (ideally) in correspondence with the actions it is set to organise. I now turn to that which is mainly considered the main justificatory context of application of the techno-medical object: the clinic.

Clinical action: diagnostic, therapeutic and preventive

Recall how, in the chapter on Heidegger, it was stated how practical interactions with material reality is the primary mode of constituting entities as meaningful to us. They fulfil some practical purpose or other. In the case of technological objects this happens through the merging of material and human agency. I now proceed with a short account of different actions made possible through the interactions with technical and technological objects within the clinical context. An object in general is thus meant to signify some stabilised pattern of action made possible through the objectification of some specific aspect of physiological function. The central notion is that such objectifications of reality make decisive differences for action. Only in the case of therapy will it be fully appropriate to speak of technological objects (*i.e.* standing-reserves) in the sense described above, as stored up agency that can be released at will. In diagnosis it may be more pertinent to speak of technical objects, i.e. as objects that lead to some further intervention and not directly to improvement. As will be seen in the following analysis, this difference is important insofar as this leaves more of the responsibility for action in the hands of the physician or the patient, i.e. further interventions come to hinge upon choice rather than material agency. Lastly, prevention may be material in which it may be described as a standing reserve, or it may take the shape of *information*.

Diagnosis. The practicing clinician finds himself between two worlds: on the one hand, that of the pure laws distilled in the laboratory and, on the other hand, the complex life-world of the patient and the clinical context as made up of technical apparatus, colleagues, administrative work and so on. In the laboratory, technological equipment and scientific methodology is used to purify phenomena from unwanted influences, so as to get to their generality. In the clinic, equipments and technologies are used to localise causes of pathology in the concrete case of the patient. *Pathology* is objectified by correlating *symptoms* as expressed in and by the patient with findings of objective *signs* gained through the use of

biochemical or genetic tests, or through the application of powerful visual technologies, like the PET-scanner, ultrasound or the CT. To a large degree, the authority of the medical doctor hinges upon the notion of a privileged access to the underlying causes of disease as expressed in the physiological symptoms:"…in diagnostication a symptom is usually considered to be an abnormal sensation *perceived by the patient*, as contrasted with a physical sign that can be seen, felt, or heard *by the examiner*" (DeGowin and DeGowin 1976). In order to relate to a previous chapter: clinical judgement aims at the identification of primary qualities in Descartes' sense, and these are by necessity established through isolation and careful analysis within the environment of the laboratory.

The *diagnostic object,* then, is obtained through a complex process of correlating a general knowledge of normality and pathology with the concrete case of the single patient. This corresponds well with the hermeneutic conception of judgement as conceptualised from Aristotle to Gadamer: it is the movement between the general and the particular, and this movement cannot itself be subjected to general rules, but relies upon the training of *judgement*. Clinical skill and judgement cannot be transmitted through theoretical learning only; it is also a matter of experience and of tacit know-how. Here is how one anthropologist describes the process of making a genetic diagnosis in the case of dysmorphology:

"The qualities that enable this [diagnosis], clinicians recognize, cannot be extracted from textbooks or found in dysmorphology databases. Clinical expertise involves something more than textbook knowledge or following the routine of history-taking, investigation, and differential diagnosis. It develops over years of clinical experience, and it is expressed in slightly different and sometimes idiosyncratic ways by different consultants. Clinical skill may enable a consultant confidently to rule out a particular diagnosis by noticing the absence of distinguishing physical features, without waiting for laboratory test results. Or it may permit diagnosis when only some of the usual features of a particular condition are present. It is also displayed through the ability to suggest a diagnosis where no one else can, or where the usual presenting features are absent" (Shaw 2003).

Hence, the skilled clinical geneticist may not have to consult with a laboratory in order to make a diagnosis. Still, this does not change the fact that the laboratory states a necessary condition for the practice of clinical judgement. Obviously, the ability to recognise a specific genetic disease on sight depends upon an intimate acquaintance with experimentally established knowledge. This is a question of knowledge about normal physiological functioning as well as knowledge of the pathological deviations from these physiological norms. As will soon be described, this entails a specifically *modern* conception of diagnostics; one in which the recognition of the pathological by necessity has to pass by an understanding

of normality as established within the laboratory. Although consulting experimentally established knowledge is not necessary in every concrete case, the knowledge of the experimenter is implemented as an essential part of the training and socialisation of the clinician.

The exercise of clinical judgement then, takes as one of its major premises knowledge established through experimental action in the laboratory. This knowledge, as already stated by Claude Bernard, is one of principles of general physiological functioning. This is how the clinical diagnosis of pathology comes to rely upon the general knowledge of the normal functioning of the organism as defined in terms of objective signs.

As clearly as modern clinical judgement cannot do without experimentally established knowledge, as clear is it that it cannot be reduced to this knowledge. And so the clinician will frequently operate with more complex and heterogeneous notions and models of causality than does the experimentalist. In the philosophy and theory of medicine, one important outcome of this difference, is the tension between the concepts of illness and disease (Wulff, Pedersen S.A. et al. 1990). In the words of one practitioner and philosopher:

"Health care practice uses the concept of causation to provide an explanation for a person's illness and to offer a theoretical rationale for action to restore health. Causation in health care is therefore a subset of causation in the broader sense. What is not always recognised is that the way causation is conceptualised in health care practice is dependent on the way illness is conceptualised. In primary care causation is usually conceptualised in terms of an holistic relationship where it at least describes, and at best explains, how two or more (and usually many more) items (states, events and objects) relate together to generate the outcome experienced as illness. This contrasts with the traditional biological model where the influence of contagionism in the 19th Century left a legacy of unifactorial causation as an ideal, even if today it is recognised that actual situations are more complex" (Tyreman 2004).

Therapy. Medicine did not prosper as a modern profession until the therapeutic revolution of the early 20th century. As will be described in some more historical detail; diagnostic skills, however good, were never adequate to redeem the great promise of medicine: to cure disease (Porter 1997).

Because pathology is caused by a deviance from normality, therapy must aim at somehow interrupting the chain of pathological causation. The aim of such intervention is to re-establish normal functioning (Bernard 1957). We may imagine different pathways by which the abruption of pathology takes place: it may be directly or indirectly connected to the causative

agent. Take the example of immunological intervention: insofar as therapy becomes a question of applying the specific antibody to its corresponding antigen, the intervention goes directly to the causative agent (by way of technological re-construction of the operations of the immunological system). In other cases the relationship is not that simple, as for instance with chemotherapy for cancer. In yet more "distant" cases the question becomes one of postponing or alimenting the effects of the pathological agents, as is the case with most treatments for HIV. In that case, although the causative agent may be identified, the actual causal pathways are not, and so therapy remains partial. As a case bordering on that of therapy, we may also talk about the *palliative* object, which aim is not to cure but to decrease suffering (pain, nervousness, depression, anxiety…).

Anyway, the primary aim here is not to distinguish between all the ways in which therapy may be accomplished, but rather to lay bare some basic premises for the social organisation of therapeutic action. Because diagnosis depends upon a previously established understanding of normality *and* a localisation of the causative agents of disease, therapeutic action presupposes the existence of both the laboratory (in order to establish physiological norms) and the clinic (to develop diagnostic skill). As stated by Roy Porter: 'The interplay of physiology, pathology and pharmacology constituted the key to experimental medicine, and each had to be a laboratory science' (Porter 2002:83).

In concrete, material terms, the therapeutic object will be more of an "object" in the everyday sense of the word; it is *manufactured* and so typically takes the shape of a pill, some substance to be injected or the like.

Prevention. Prevention is also derived from a previous understanding of pathological deviations from normality. The central difference (from the point of view of action) is *temporal*: prevention aims at interfering before the pathological fact and not after. Prevention objectified may be both material and intellectual.

The classical example of material prevention is vaccination, a direct physiological measure. Vaccination is a technological object in the Heideggarian sense, it is a standing reserve to be released at will. The effect of prevention, however, is not experienced as a positive manifestation; it is rather to be described as the *absence* of some effect (disease) that could

otherwise be expected to occur. In other words: prevention is a matter of avoiding risks. Again, the object may be directly or indirectly applied to avoid disease. Injecting antiserum into the organism aims at interference-before-the-fact, to block the future action of an external agent, the antibody. Other preventive measures may be applied to the environment of the exposed organism rather than to the organism itself, as typically found in hygienic interventions to neutralise pathogens in the water supply, build sewerage systems, or to clean the air or the soil.

Non-technological interventions may aim at social prevention of pathology; improving living conditions and the likes. In that case, it is more a question of applying *information* as a means of prevention, and not some direct, technological intervention with highly specific aspects of the environment. Since the time of Rudolv Virchov, this has been one important task of social medicine. As will be seen in the analysis of genetic and genomic medicine this mode of action is becoming more and more wide-spread (as a part of the wider paradigm of preventive medicine).

I now continue to expand the framework even further, to encompass factors that have been regarded as "external" to the concerns of research by such different perspectives as classical epistemology, the ethics of research (Merton, Tranøy) as well as the micro-sociological approaches described (Knorr Cetina, Rheinberger).These are, of course, political and legal principles of action.

Organising legal and ethical principles

Large parts of the previous chapter went to transform the Heideggerian conceptions of *Bestand* and *Gestell* into terms that can be used to analyse actual experimental intervention aiming at the manufacture of stable and standardised techno-medical objects. However: Transferring the Heideggerian philosophy of Being-in-the-World to the production of scientific knowledge in second modernity lays bare a fundamental weakness of that philosophy: Whereas in a pre-modern, archaic world, we may presuppose the ready-to-hand, i.e. the importance of things and tools, as prior to domains such as politics, economy and industry, and still get away with it, this will not suffice for the analysis of knowledge-based practices in (second) modernity. Today, more clear than ever, we cannot ignore the political character and constitution of science. Most large-scale research, like the Manhattan project, research in high-energy physics or the Human Genome Project presuppose major political

commitments for their realisation. Moving backwards through history: The project of building the nation state cannot be subtracted from the scientific enterprise any more than science can be subtracted from modernity (Giddens 1990). And, going even further back: the projects of science, wealth accumulation and political rights all find themselves at the centre of the social contract as articulated by Locke, and they are all intimately linked to the notion of the agent as a rational actor (Locke 1966).

Politics and science are mutually supportive and dependent, though strangely separated at the same time. Just think about the necessity of engineers and medical doctors for the projects of nation-building in the 19th and 20th centuries, as well as the necessity of the national state in granting to those professions legitimate monopolies over their respective action domains. In other words: science and politics have co-evolved (Latour 1993).

However, a great number of theorists converge on the finding that the times of smooth co-production of scientific and social order may have come to an end (Beck 1992; Latour 1993; Nowotny, Scott et al. 2001; Jasanoff 2004). The changed position of the nation state within the global economy is one significant fact about the matter (Beck 1993, 2001). Along with this deterioration of previous categories of legitimacy, a long-held dogma is questioned: the presupposition of politics and science as sharply distinct domains of action and organisation. Not infrequently, this new constellation of things is itself propelled forward by the strengthened positions of industry, economy and technology into the previously stable categories of politics and science (Etkowitz and Webster 1995). These developments blur previously stable categories of legitimacy, such as for instance those between public and private funding, or that between basic and applied research, or they question the nature/culture opposition more directly, as in the case of the patentability of living things.

Relating to the methodological choices of this project, this entails that we cannot allow ourselves the naivety of treating legal and political modes of action as derivative of or historically secondary to scientific practices (although the standard modern solution claim exactly that procedure as its mark: first, find out what the object is like, then decide, in terms of values and political considerations how to deploy it). This is especially true of the principle of patentability, which has significantly altered the pace and nature of basic research in the biomedical sciences (Krimsky 2003).

Relating to Heidegger the socialisation of science and technology revealed the inadequacy of describing these in terms of historical epoch or technological determinism (modernity as the epoch of the *Gestell*). In the previous chapter, therefore, I tried to recast his philosophy of technology in more sociologically oriented terms, like that of the counterfactual organiser. When socialised in this manner, it remains hard not to take notice of the specifically political character of modern science and technology: new technologies, like biotech, computers or semiconductors, have been called upon to replace old industries like chemicals, cars, or even oil (Doremus 1995). And genetics and reproduction technologies have raised the issue of the worth of the unborn, or of genetic deviance, in a new context. What is offered us by Heidegger is a rather *linear* representation of technology as determinant of the moral or political sphere. But we cannot accept such dogmatic conclusions, and so the communicative framework should be further expanded.

I therefore continue to sketch out some basic methodological features of what I have just argued: that patentability and autonomy are not to be treated as derivative on science or technology, or as totally independent, for that sake, but rather as two sides of the same coin: science and morals, nature and culture. Politics are themselves capable of (relatively) autonomous intervention to change the course of science and technology. There is, in short, no reason to treat the one sphere as principally prior to the other, or to regard them as dealing with absolutely separate domains. This is reminiscent of Latour's general principle of symmetry. But in accordance with my previous critical remarks, the field is investigated from the point of view of social action and hermeneutics, and not from Latour's field ontology. I start out with a standard account of action according to legal rules and principles, before I say something more of the intersecting of the legal and the political with the scientific taking place in second modernity and some of the challenges thereby raised.

Legal rules and principles according to Hart and Dworkin

I have already spent some time trying to establish a hermeneutic framework for the analysis of the techno-medical object and its organisation as centred round the counter-factual organiser. But it has also been claimed that the concept of counterfactual organiser is not restricted to the domain of science and technology, but can also be applied to the domains of law and politics. Also here they entail presuppositions about agency: in the case of autonomy, it is the general stipulation that the single individual is capable of rational self-determination (Kant 1968). Applied to medical ethics this notion implies that the patient should determine what is best for

him or her in a context of research or clinical treatment (Beauchamp and Childress 2001). In the case of patentability it is the expectation that a contractual relation between inventor and society will turn out to the common good due to the workings of the market (Etkowitz and Webster 1995). In both cases, law instigates itself between the involved actors and ascribes rights and duties (more or less) in accordance with the relevant principles. In this section I revisit some central elements within the sociology and philosophy of law, addressing the issue of legal rules and principles as social action.

Law, said H.L.A. Hart, has the character of power-conferring rules (Hart 1961). It ascribes powers to act in certain ways to legal subjects (like for instance the Parliament). The primary function of law is not that of giving orders to the citizens or of ascribing punishment in case of breach. The primary function of law is to order and co-ordinate actions among the citizens, and between the citizens and the state. In most cases legal rules have little to do with punishment and orders, but much to do with how we actually make our way in modern society: getting a driver's license will give me the right to drive a car, but also the duty to respect the traffic regulations; if I change my nationality from Norwegian to Spanish, I will be a legal subject to Spanish rules and regulations. I will have the duty to pay my taxes to the Spanish government, but I will also get the rights that come with a Spanish citizenship. The legal system, said Hart, functions mainly by conferring to subjects the power of entering upon legal arrangements or contracts ascribing rights and duties. Speaking with Giddens, law may be seen as the most basic social mechanism for integrating the *life politics* of the citizens (Giddens 1991). Although these accounts may be based upon optimistic accounts of the capabilities of personal autonomy, it is clear that laws in many cases have the power of providing individuals with opportunities for action. One central function of legal rules is to provide legal subjects with more or less stable and predictable frameworks so that ordered social action and planning becomes possible:

> "to promise is to say something which creates an obligation for the promisor: in order that words should have this kind of effect, rules must exist providing that if words are used by appropriate persons on appropriate occasions…those who use these words shall be bound to do the things designated by them. So, when we promise, we make use of specified procedures to change our own moral situation by imposing obligations on ourselves and conferring rights to others; in lawyers' parlance we exercise 'a power' conferred by rules to do this" (Hart 1961:43).

Although Ronald Dworkin may be said to have continued Hart's sociological approach to law, he also sharply criticised it for being too simplistic. I will not go into that debate here

(i.e. Dworkin's critique of legal positivism), but just confine myself to the expansion of Hart's notion of law as a system of rules. Hart's notion, says Dworkin, is flawed because, by its exclusive focus upon rules it fails to observe the presence of the more complex phenomenon of *principles*. Logically speaking, whereas rules have an exclusive either-or character (one has a right or one has not), principles are less clear-cut in that *different* rules may legitimately be derived from them. Although part of the legal and political system, they "do not set out legal consequences that follow automatically when the conditions provided are met" (Dworkin 1977:25). Hence, there may be reasonable disagreement as to the application of principles to a single case, and in every instance discretion and judgement is required to determine whether or how a principle should be brought to bear on a case: "All that is meant, when we say that a principle is a principle of our law, is that the principle is one which officials must take into account, if it is relevant, as a consideration inclining in one direction or another" (*ibid*., 26). Hence, principles may be closer aligned to deeply embedded cultural, political and legal values, and as such they distinguish themselves from rules by carrying normative weight that cannot be fit into the all-or-nothing character of rules. In logical terms: legal rules may be derived from principles, but principles cannot be derived from legal rules.

Principles, in contradistinction to legal rules, cannot be confined strictly to the legal system, but have their relevance and importance from close connections to other cultural and political currents: "The origins of…legal principles lies not in a particular decision of some legislature or court, but in a sense of appropriateness developed in the profession and the public over time. Their continued power depends upon this sense of appropriateness being sustained" (*ibid*., 40). Hence, although they may remain stable over long periods of time, as for instance many of the political freedoms, principles enjoy a much more fleeting existence than do rules:

> "…we could not devise any formula for testing how much and what kind of institutional support is necessary to make a principle a legal principle, still less to fix its weight at a particular order of magnitude. We argue for a particular principle by grappling with a whole set of shifting, developing and interacting standards (themselves principles rather than rules) about institutional responsibility, statutory interpretation, the persuasive force of various sorts of precedent, the relation of all these to contemporary moral practices, and hosts of other such standards" (*ibid*.)

As will be seen, the two principles of autonomy and patentability are principles in Dworkin's sense. In nothing but the most obvious cases definite rules can be inferred from them, and in the overwhelming number of cases considerable negotiation between different actors are necessary to arrive upon more or less specific rules of action. For instance, it took many years

to establish the rule that informed consent was to be required where research upon human subjects contained the slightest risk for the subject. And only after the establishment of that rule it was inferred that it was derived from the more general principle of autonomy (Jonsen 1997).

Importantly, on Dworkin's account there is a close relationship between *policies* and principles, even so much that they at times may become impossible to separate. That is also very much the case with autonomy and patentability. When the patentability of living organisms was introduced by American courts in the early 1980s, it was closely related to the political initiative to transform and renew industry through the commercialisation of science (Hughes 2001). After this short account I now turn to one of the particular and most peculiar marks of second modernity, namely some of the ways in which the scientific, the legal and the political come to intersect in (seemingly) new ways.

Granted these general accounts of law and its role in organising and facilitating social action, peculiarities arise when applied to fields opened up by novel and fast-expanding technologies: First, as described by Hart, one main purpose of legal rules is to supply predictability and stability to social action. This, however, is hard in fields in which there may be few precedent cases upon which to rely and an even scarcer understanding in the general population from which to draw legitimacy. Second, in strong relation to the first point comes the strong inclination towards basing this kind of legal decisions and legislation upon premises taken from experts, i.e. natural scientists (Jasanoff 1995; May 2004). This again poses a number of further problems of both practical and principal character: will the decisions carry sufficient democratic legitimacy? What about the cases in which no consensus is to be found among experts: Who are we to rely upon? Can experts within very narrow fields be trusted to be experts also in wider social issues, or may it even be that these experts are exactly the ones that are not to be trusted where broader issues are involved? (Veach 1995). Last, but not least, many of the questions posed by new technologies also carry strong political implications and symbolic significance. As described by Dworkin, it may be difficult to distinguish between policies and legal principles, and this may be even more so in the cases with which we are here dealing. For instance: In the case of new reproductive technologies and stem cells research we witness how these issues range high on the political agenda, and this may not contribute to greater stability.

Contextualising autonomy and patentability

It has already been described how organising principles of the life-sciences may be put into context. In the case of the gene, I will take it that there is indeed such a thing as DNA, described by Watson and Crick in 1953 and that this was an important event in the founding of a new discipline, molecular biology, which would come to act as the representing agency of physiological function as conceptualised through the central dogma, articulated by Crick in 1958. Although the representing principle will frequently be confounded with its reference, DNA, this is a mistake: there is no pure correlation between the concept and its phenomenon (Kant 1968). Furthermore, I have argued that for the sake of social analysis we cannot rely upon realist assumptions taught in science class or by classical epistemologists; the real reference of the organising principle is the actions that it makes possible, and the representing agency is not the concept but the scientific community.

Now, we may make similar moves with the legal and political concepts of autonomy and patentability. Also these principles organise social action across a broad range of disciplines, life-worlds and professions; also these have their representing disciplines referring to specific domains of action. What is more, just as the central dogma may be traced right back to the anthropology of the 17th century, so autonomy and patentability have deep cultural and political roots. Indeed, both are to be found at the centre of the social contract as articulated by Locke, the founding father of liberal democracy. Furthermore, also patentability and autonomy make counterfactual statements about agency and causal relations in the world, although in a different and less precise manner than is the case with the central dogma and physiological functions. These are not simply observations or neutral reports of states of affairs existing "out there"; they are deep-held convictions residing at the roots of western culture. This is, I take it, one main reason why they are called upon in order to regulate in the cases of novel technologies: in cases of uncertainty we try and stick to formulas that have worked before, not the least because these may induce legitimacy due to their cultural importance.

I will return to some of these reflections in the chapters on patentability and autonomy. For the moment, however, I will try and say something more about how we may address the concrete contexts of the two principles. To what or to whom is it that they refer? By who are they represented?

In the case of *autonomy* it may be said that it refers to every citizen finding him or herself within some western democratic constitution, and that this has been so, at least ideally, since the introduction of political rights. However, what is of interest here is how the principle can be said to be thrown into a new context, the medical; how it has served as a mean for negotiating new social and material relations and ways of action, and how it has come to intersect with domains of action traditionally belonging to medicine and to science. This is of course also the main reason why the shaky foundations of the nature/culture divide has been so strongly emphasised earlier on: at least on the face of it, it seems that some deep-held convictions about the nature of things has been challenged. In short: autonomy was introduced in order to challenge the view held for more than two thousand years granting the sole authority of the therapeutic encounter to the medical doctor. In the face of challenges posed by technological and institutional growth it was surmised that the medical doctor no longer was the natural authority in matters dealing with health and sickness, and that a wider range of decision-makers had to be introduced into the decision-making process. This change was further propelled by the political climate of the 1960s, emphasising minorities' rights, self-determination and anti-authoritarianism. The language of rights to self-determination was further articulated and stabilised by bioethicists and lawyers in the 1970s and it came to make up a central principle in the re-negotiations of the relationship between the scientific and the medical worlds on one hand and the patient or research subject on the other. Therefore: although the principle of autonomy, which eventually came to make up a cornerstone of bioethics as well as central parts of health legislation, instigates the patient as the central decision maker, it is clear that in reality it should be seen as part of a much wider field in which a number of actors, disciplines and professions readjust to technological and social change. At the same time, the interests of the patient should indeed be held up as a main principle for assessing developments, for making strong evaluations. Autonomy, then, as both a legal principle and a tool for policy-making is situated within a complex net of actors and disciplines taking shape after the Second World War, it is articulated by bioethics and health law. As a normative starting-point, we also state that it refers itself to the life-world of the patient and to his or her well-being.

Similar conclusions may be drawn regarding patentability: it was part of industrial politics and regulation since the time of the industrial revolution, but it did not make up a central concern to life scientists until the 1970s when the economy entered the laboratory through the patenting of recombinant DNA technologies. It has become a central tool for policy-making

in the face of emerging (global) industrial and economic landscapes, and it is effectuated by a professional group, economical law, although also subject to considerable influence from politics and from the economy itself. Rather than continue this line of thought, however, I would like to make a short hermeneutic reflection upon the close ties between economy and technology. I return, therefore, to the language of Heidegger:

Similar to technological power, we may also regard the position of economic or other valuable property as a standing-reserve. Indeed, the language suggests that Heidegger has taken the metaphor directly from economy: *Bestand*/*standing reserve* is a surplus of resources that has been stored up through the use of standardising media and that can be released at will. Hence, the economy, in a primitive form, may even be the origin of the conception of the standing reserve. Furthermore, in both the case of technology and of money, numerology and quantification play significant parts by serving the medium through which the standing-reserve is quantified and rendered capable of being handled intellectually. This is also what renders both money and technology de-contextual beings: they may be transferred from one context to another. Out of this exchange they may gain or lose value, but their function and the conceptions through which their functions are conceptualised (standardised) remain more or less the same.

Thus, whether we regard economy or technology as the primary version of the standing reserve may be a matter of convention, and not of absolute priority. Both are ways of storing up that seem to have a certain catalytic effect on the other, both may embody potentially powerful modes for enhancing action and agency, and both are in principle exchangeable for each other.

Indeed, technology *is* the vehicle of an intensified exchange between economic and natural resources, an exchange that is radically intensified in second modernity. Before large-scale technologies, providing standardisation on a wide basis entered the field of the life-sciences, there was no strong relation between the economy at large and scientific or medical practice. For instance, the general practitioner, although operating in a free market, would only on very rare occasions be a wealthy man (Rothman 1991). Before the strong expansion of medicine following the therapeutic revolution and the building of large hospitals, there was no strong connecting principle between physiological function and the function of the economy.

In second modernity, technology has decisively connected the domains of two of our counterfactual organisers: the hidden hand of the market (patentability) and the hidden design of physiological functioning (the genome). The intrusion of the economy accommodated through the principle of intellectual property rights has been significant enough to cause serious concern about the integrity of both science and medicine. In a 1982 commentary in Science it was stated that:

”Scientists who 10 years ago would have snubbed their academic noses at industrial money now eagerly seek it out...The present concentration of industrial interest in academic science is generating no small amount of concern about whether the academy is selling its soul” quote from (Andreoli 1999).

After these brief remarks the analytical framework may be displayed as follows:

Representing discipline	**Action-organising principle**	**Reference/context**
Molecular biology	*Central dogma*	DNA/physiological function
Economical law	*Patentability*	Commodities/markets
Bioethics	*Autonomy*	Patient/life-world

I now turn to some further considerations upon how principles like the above have entered society during the course of modernisation. I keep basing the exposition upon sociological theories of reflexive modernisation and upon hermeneutics, and I try to further merge the two frames of analysis.

The socio-material contract

There is a peculiar fact about the modern production and distribution of knowledge: it proceeds on the general assumption that whereas science deals with facts, politics and law deal with values. We have seen the contours of this division of labour in the anthropology of Descartes, where dis-interestedness towards the body and the world is constitutive of the calculation of how to pursue our worldly interests in the best manner. And we see it at work in the production of knowledge: great resources are called upon for the sake of creating new knowledge, but the main source of legitimacy of that knowledge remains its character of a disinterested representation of nature’s workings offered us by science. How can something be regarded as non-biased, and still be invested with so much value, culturally, politically and economically, as science and technology?

This way of producing and distributing knowledge is, I will argue, one of the main obstacles towards overcoming the problems that come with socialised science: Science and technology, propelled forward by strengthened alliances to the economy, transform culture and society with unprecedented speed. Still, large parts of the social and humanistic disciplines would rather ignore that fact: they leave science and technology to scientists and engineers and work on social and cultural issues "proper". Hence, knowledge of nature and knowledge of culture usually concern themselves with widely differing fields:

> "As in the famous Cartesian mind-body dualism, there are two realms whose natural unity is apparently broken into two modes of being; or at least, into two kinds of knowledge. In the familiar environment of the West, ideas or theories of the natural world seem to run along their own course and to reflect an internal, unfolding logic isolated from the historical or social contingencies that interest the historian" (Figlio 1977)

However, parts of the disciplines we may term social and cultural have turned their attention towards these problems: for the law, of course, technological developments cannot be ignored. Unlike most social and cultural sciences, law *has* to intervene, and it is forced to face up to social problems created by science and technology. In addition we have a growing sub-discipline of philosophy, namely bio-ethics, which has come to occupy itself with practical moral problems created by advances in medical technologies and in the health care system in general. Not the least, because bioethics has concentrated upon issues of direct relevance to the interactions of law and clinical practice, it has made itself a socially relevant discipline, involved in negotiations over research practices, patient's rights, clinical dilemmas, and so on[25].

The legal profession and the discipline of bioethics, while intervening with the practices of the life-sciences, to a large degree do so through transformed versions of the language of *rights* as instigated by philosophers in the 17th century. This comes down to the effect that whereas the language of rights, originally constructed to deal with the political sphere only, increasingly intrude also on the field of science, it still remains articulated within the language of the legal and political spheres. However, in so doing, rights by and large accept the accounts of the natural world granted them by science (these are, after all, objective), and so the question

[25] Science and technology studies (STS), however, have so far had their domain of action *mainly* restricted to academic circles. This is to be lamented, insofar as these offer perspectives carrying a much wider scope of social and cultural issues than does law and bioethics, and insofar as they do not generally proceed according to the general assumptions laid down in the modern fact/value scheme. But then again, that may be exactly the problem: that of falling between categories of both thought and action.

becomes one of rights ascribed to a subject on the basis of a specific state of the world as described by science. For example, I have the right to receive proper information about the nature of the genetic test I am about to take, as well as the possible consequences it may have for me, before I take the test. In Norway, genetic testing comes with genetic counselling as a right for the patient and as a duty for the health care system.

Following Shapin & Schaffer (1985) and Latour (1996), this state of affairs may be analysed by recourse to negotiations among empiricist philosophers of experiment and rationalist strands of political philosophy in the 17th century. In the face of continuing social unrest and religious wars, philosophers of both schools sought out methods for arriving upon unbiased truth about nature and society. Two solutions emerged, sharply at odds but oddly complementary at the same time: One was that of physical experimentation (Boyle); the other was that of the political sovereign (Hobbes).

According to the experimentalist version of truth, the only safe method of reaching mutual agreement would be to let nature speak for herself, and for the scientist to be her witness. As nature is silent, however, that intervention called the *experiment* was required to help nature give her secrets away. The virtue of the carefully conducted and constructed experiment would be that it left no doubt in the mind of the spectator. Hence, the scientific object is given a new function, insofar as it becomes the silent representative of nature and the final witness of truth (Latour 1993). On the other hand, this newly established sphere of agreement was to be sharply separated from politics or from traditional scholastic philosophy, domains in which strife, disagreement and un-order were expressions of the general (political) conditions of the times.

Thomas Hobbes, on the other hand, constructed an altogether different way of representing: the sovereign, invested with the right to represent everybody through the monopoly of social power: the head of the state, invested with the powers to create social order. The contract between the sovereign and the people would come about as the result of a rational calculation on the side of the citizens: to give away part of their freedom in exchange for protection of life and property. Only by submitting to one total power, could the social and political spheres be brought under control (The contract could be reversed under extreme conditions where the sovereign did not fulfil his duties). This transfer of power could only take place under the condition that other authorities, such as God or natural spirits, were dispelled from the

political altogether. Under these conditions, the claim from the experimentalists, that the experimentally established object be the last authority on any matter, represented a decisive threat to the authority of the sovereign: no one could know in advance which truths the object would yield.

This opposition was not solved. Rather, the gradual acceptance of both views came to constitute a mutually exclusive contract: to give to science what belongs to science, and to give to the sovereign and the subjects of the state what belongs to politics (Latour 1993). Both positions shared a commitment to proper *method* as a way of ridding reason of unwanted, external influences. Furthermore, the commitment to scientific method issued in mechanistic explanations of the political as well as of the natural, as was common for the new natural philosophers. The disagreement was *how* to conceive of mechanism, by mathematics (Hobbes) or by experiment (Boyle), and to *which spheres*, the social or the natural, mechanistic explanations were to be deployed (Shapin 1999).

I now proceed by sketching out some of the consequences this differentiated delegation of authority was to have for the organisation of action. The sketch bases itself upon arguments that should be well-known to those who have followed hermeneutic and practical philosophy through the last half of the previous century.

Expert and lay, universality and contextuality

Obviously, science, politics and society have changed considerably since the times of Hobbes and Boyle: the sciences have become powerful tools of intervention with both the material and the social, and we have had representative democracy and the division of powers. But the significant point is that the strange separation between fact and value, scientific truth and political rights, has prevailed right up until today, although within new configurations.

Within their separate domains they have served as vehicles for the fostering of whole professional groups: engineers, medical doctors, lawyers and politicians. The professions have come to serve as the main representatives of different aspects of reality: nature on one hand, legal and political rights on the other. In respect of being legitimate representatives of the different spheres of reality, specific domains of action have been singled out as legitimate domains of intervention to promote social order. In other words: the natural and the cultural have served as different, though complementary, sources of legitimacy in the ongoing

rationalisation of society (Weber). During the modernisation of western societies, sources of legitimacy were increasingly conceived of in terms of universal claims to truth and validity. In action, universality spells out as the application of the smallest number of principles to the largest number of cases. This is also where the issue, so much debated in recent philosophy, between formal and substantive justification[26], enters the picture. When a rising number of cases are to be submitted to a decreasing number of principles, tensions arise between universal principles and the need for concrete, case-by-case knowledge and argumentation. Hence, what took place through the socio-material contract was very much an elevation of abstract reasoning over contextual knowledge:

"The contrast between the reasonableness of narratives and the rigor of formal proofs, between autobiography and geometry, is the contrast between the "soundness" of substantive *argumentation*, which has the body and force needed to carry conviction, and the "validity" of formal *arguments*, whose conclusions are determined by the starting points from which they are deduced. There is a parallel contrast between our local knowledge of the patterns we find in concrete events, and the universal, abstract understanding embodied in purely theoretical points of view. The substance of everyday experience refers always to a "where and when": a "here and now" or a "there and then". General theoretical abstractions, by contrast, claim to apply *always* and *everywhere*, -and so –as Tom Nagel points out – hold good *nowhere-in-particular*" (Toulmin 2003:15-16).

Modernity has institutionalised, standardised and materialised universality, in the sense that universal laws of nature and the universal rights of the citizens were made bases of decision-making within the professions. Hence also the organisational necessity of elevating counterfactual organisers to legitimate principles of social and material intervention: as no two cases are exactly the same, the principles underlying material and social agency, like autonomy (Kant), the hidden hand of the market (Smith) or the hidden design of physiological function (Bernard), would have to serve as principles for the organisation of action. This also allowed for ideas of agency, and for technological objects, to be transported across distances of time and space, and to be re-embedded within different contexts from the ones in which they arose.

However, as indicated by the quote from Toulmin, the standardisation of action-organising principles has come at a price: the (partial) forgetting of the contextual grounding of knowledge, so necessary for the redemption of the fundamental (human) interests that knowledges are expected to promote and legitimate, for instance those of securing social

[26] See for instance (Habermas 1981; Habermas 1992). Although I here refer to the distionction in its modern sense, i.e. as *argumentation*, it may be traced right back to Aristotle's distinction between technical (*Techne*) and practical skill (*Phronesis*) (Aristotle 1955).

order and human health. For whereas universal knowledge claims can be validated through experimental testing, theoretical or ethical justification, this will not suffice to justify the social legitimacy of the actions that universal claims are set to organise, nor of the social or material interventions carried out in order to reach those goals.

The socio-material contract and its division of reality into two separate spheres, each to be represented through universal propositions, was accompanied by a removal of the bases for acting, knowing and choosing: from the life-worlds and into abstract, knowledge-based systems of action. This entailed an attempt at excluding the *body* as the seat of values and of cultural and practical skills, for the purpose of promoting secure knowledge within the professions. It represented, simultaneously, the removal of the bases of public decision making out of historically and traditionally mediated structures of action and into the rationalised structures of abstract systems. Politics and law become the spheres of dis-embodied and abstract "values" recast in a language of rights, medicine and the sciences the spheres of "facts" of the mechanistic functions of the body.

For better and for worse: a removal of the knowledge bases from the life-worlds of the citizens, now to be intermediated by experts through abstract systems of acting and knowing. For instance, whereas the "right to property" in pre-modern societies would reside in networks and relations within local communities, for instance the "right" of the poor farmer to some of the crops cultivated on the land-owners' property, today property claims can be put forward on a global scale through the modernised language of intellectual property rights. Today, it is fully possible to infringe on the property of another, purely by using some product in an unknowing manner, as for instance non-licensed software or a genetic test. Or, to take another example: think about the rights that come with nationality. It makes quite a difference, in terms of formal possibilities for action, whether one is a citizen of China or of Denmark. These possibilities for action are all caught up in a number of rights and duties channelled through the administrative and legal systems of the respective countries (as well as the international institutions or agreements entered upon by the different countries).

Trust in universality?

Whereas knowledge of ethical, legal and political principles found their ways into the legal and political systems of action, and knowledge of nature went into the sciences, medicine and engineering, the contextual and fleeting knowledge that can only be gained and trained in the

encounter with the life-world was de-valuated *qua* legitimate source of knowledge. Hence, the investment of trust in the natural and the political, constituted through the socio-material contract, would come to mean a transfer of knowledge: out of traditionally organised societies and into abstract expert systems. But this did not and could not entail the replacement of structures of abstract knowledge for communal relations in pre-modern societies. In modern societies, the question of *trust*, far from having been replaced by universal systems of knowing and acting, may be more important than ever:

> "In conditions of modernity, the future is always open, not just in terms of the ordinary contingency of things, but in terms of the reflexivity of knowledge in relation to which social practices are organised. This *counterfactual* [my emphasis], future-oriented character of modernity is largely structured by trust vested in abstract systems – which by its very nature is filtered by the trustworthiness of established expertise. It is extremely important to be clear about what this involves. The reliance placed by lay actors upon expert systems is not just a matter –as was normally the case in the pre-modern world – of generating a sense of security about an independently given universe of events, as a result of the continual reflexive implementation of that very knowledge. One of the things this means, in a situation in which many aspects of modernity have become globalised, is that no one can opt out of the abstract systems involved in modern institutions. This is most obviously the case in respect of such phenomena as the risk of nuclear war or of ecological catastrophe. But it is also true in a more thoroughgoing way of large tracts of day-to day life, as it is lived by most of the population. Individuals in pre-modern settings, in principle and in practice, could ignore the pronouncements of priests, sages, and sorcerers and get on with the routines of daily activity. But this is not the case in the modern world, in respect of expert knowledge" (Giddens 1990:83-84).

According to Giddens trust is one central medium through which expert knowledge is re-embedded within the life-worlds. For instance: changes in the scientific and technological bases of medicine instigate renegotiations of the relationship between the clinic and the life-world of the patient. Throughout these renegotiations, the relation of trust between expert and lay are alpha and omega to the continued functioning of legitimate social institutions. Genetic counselling that comes along with genetic testing, as well as the new discipline of bioethics are expressions of this state of affairs (Toulmin 1982; Rothman 1991; O'Neill 2002).

These institutions, as argued, exist in a tangle between universal principles and the need for contextual understanding, a tangle which may be pulled tighter by constant pressures from economy, industry and politics of international competitiveness. Due to time pressure as well as a general increase in the shear amount of knowledge to be handled, the *need for universality* also increases. Hence, modern institutions are faced with rising demands for universality and contextuality at the same time. This means that the good understanding and

judgement, both of expert and lay, are being constantly challenged by the dynamics of second modernity.

In this context, where new technologies are introduced rapidly and without anything approaching overview of the social, cultural or medical consequences (Fischer and Welch 1999; Deyo and Patrick 2005), it may be far fetched to talk, as does Giddens, about trust as actively and rationally invested (by the public) in the social institutions and expert systems (Giddens 1991). For Giddens expert knowledge comes through as more of a positive resource than as something that is simply imposed on (more or less) un-knowing subjects (Giddens 1991). As will be seen, especially in the chapter on patient autonomy, this does not pose a realistic image of expert and lay knowledge; it remains too dependent upon the rationally calculating agent (Beck, Lash et al. 1996; Wynne 1996). In this particular context, Brian Wynne may be more on the mark in describing trust in new technologies and expert systems as "virtual trust", as based upon an "as-if" clause that is more grounded in dependency and necessity than in rationally calculated possibilities for action (Wynne 1996). I have already presented the critique directed at Giddens and Beck from social constructivists like Lash and Wynne, and I have argued that in the case of Beck's theory it is misguided. For the present project, the *main* question does not concern the character of trust, but rather the distribution of *knowledge and ignorance* (*Wissen und nicht-Wissen*), and their implications for action. This strategy is more reminiscent of Ulrich Beck's approach than those of Wynne, Lash or Giddens: "The crucial issue of reflexive modernization…is this: how do "we" (experts, social movements, ordinary people, politicians, not to forget sociologists) deal with our unawareness (or inability to know)?" (Beck 1998:102).

In trying to come to terms with Beck's question, I have introduced the hermeneutic dimension, in which qualitative distinctions are made between different *kinds of knowledge*. Thus, I also take it that the question concerning trust, rather than being placed at the basis of the analysis, is also a question of how to establish more rational social institutions, more adapted to uncertainty and unknowing, i.e. the counterfactual character of modernity. Indeed, within the hermeneutic tradition there is a long held basis for contrasting rational-calculative interaction and communication with more substantially rational notions of action and communication (Taylor 1971-1972; Habermas 1981; Toulmin 2003). This dimension, which we may now place on the interface between the "system world" and the life-world, is used for all it is worth by Wynne:

"Through their rationalist discourses, modern expert institutions and their 'natural' cultural responses to risks in the idiom of scientific risk management, *tacitly and furtively impose prescriptive models of the human and the social upon lay people, and these are implicitly found wanting in human terms*" (Wynne 1996).

The main risks of second modernity, says Wynne, are those imposed on social identities by rationalistic and technical models of human agency. However, true as this may be, Lash and Wynne's notions of social constructivism and the methodological program of ethnography tend to ignore a central issue: the instrumental character of expert knowledge, with all its reductionist and rationalist assumptions, in many cases *works*. That is, in many cases expert knowledge supplies people with desired and sought-after goods, for instance vaccinations against common diseases. Hence, public expectations to expert systems are *already* caught up in complex networks of dependency and reliance. Acknowledging this fact, and acknowledging that important aspects of public institutions are indeed strongly instrumental in character does not mean that one endorses the image of the human agent as mainly rational and calculative; it means that one accepts that parts of human life is concerned with instrumental pursuits of necessary goods, like food, health and money, and that central parts of expert systems are constructed to serve those needs. True, a lack of trust may result from overtly instrumental attitudes of experts towards the lay public. But a similar distrust and a lack of legitimacy may also arise from the failure of expert systems to provide important social goods, and this is indeed one main argument in Beck's theory: in second modernity there is a real danger of the side-effects of expert knowledge outpacing the goods that supposedly come from such knowledge and from new technologies (Beck 1998). But to present this mechanism as the outcome of a simple calculation of risks versus possible advance, as done by Lash and Wynne, remains a too simplified image of social action held by neither Beck nor Giddens.

Authors like Wynne and Lash, along with many other proponents of ethno-methodological or micro-sociological methodologies in science and technology studies, typically forward *local* strategies and contextual knowledge as "real", as opposed to (socially) constructed regimes of expert knowledge. On the other hand, modernist readings would tend to emphasise, as does Giddens, the positive character of new possibilities offered to us by science and technology and the increased autonomy granted to the individual.

In what follows, I want to cast a (hermeneutic) glance upon what may be found *between* these traditionally opposed strategies. According to Beck, simple modernity thrived on excluding its own basis of knowing and acting. One central mark of second modernity is that what has been excluded, for instance the contextual character of knowledge, now re-appears in the middle of modern practices themselves (Beck and Bonss 2001). In this project, that presupposition is coupled to and attempted confirmed through recourse to a hermeneutic conception of agency and social action: modern forms of knowing and organising typically proceed on "thin" notions and presuppositions of social and material agency (Geertz, Oakeshot), thereby excluding the wider environment, culture and the body, what Clifford Geertz would call "thick descriptions". Hence, the theory of reflexive modernisation is coupled to a normative and hermeneutic call for knowledge-based institutions that provide time and space for critical reflection and experience across disciplinary and professional borders, the ultimate purpose of which is to develop what Aristotle termed practical wisdom, or *Phronesis*. A central asset of that capability is that of *good judgement*, essential to the negotiations taking place between expert and lay, system and life-world.

Judgement: modernity's excluded third?

Judgement, according to the hermeneutic tradition, is the movement of the intellect between the general and the particular[27] (Gadamer 1960). Both legal and medical reasoning are prime examples of such operations of human knowing and acting (Gadamer 1960; Cassell 1991). The strange thing about judgement is that, whereas it works by applying general principles to particular cases, this skill of the human mind and body cannot itself be subjected to rules (Wittgenstein 1953; Aristotle 1955; Johannessen 1990). Judgement is intrinsically interwoven with practical skill and training, and only the experienced practitioner knows how to move between the different layers of being and generality in order to secure the best possible outcome. The beginner, on the other hand, has to rely upon theory and advice from more experienced practitioners for his or her advancement within the field (Dreyfus and Dreyfus 1986). As modernity progresses, the distance between the universal and the contextual may become harder to negotiate. Thus, *good* judgement is continuously challenged.

That is not the least so because the two poles of representation sketched above do not, within their idealised conceptions of reality, really recognise the *fundamental* value of judgement to

[27] Another word for judgement may be good common sense, in the English empirical tradition primarily connected to *sentiment* rather than to intellectual representations (Gadamer 1960).

social practice. Rather, judgement is regarded as firmly situated *within* the schemata of universal principles, as detrimental to the practical *application* of such principles, but not to their establishment. That is, the fundamental laws of nature and the rights of men are, due to their universal character, in principle beyond the uncertainties of daily experience and historical contingence. Whereas judgement obviously cannot be excluded from fields like law or medicine, practical skills are constantly challenged by universal claims constructed to promote certainty and cleanse the sources of legitimate knowledge of uncertainty.

This is perhaps most easily seen in the repeated attempts at overcoming un-warranted influences on the understanding of disease, which spells out as the attempt to transform medicine from *art* to *science* (Bernard 1957; Cassell 1991). As conceived by Bernard, the clinical application of scientific principles could not, and should not, be cleansed of uncertainty and complexity, but the *basis* for clinical intervention, delivered through experimental action, could (and should). Similar developments are to be found within the art of building and constructing, which in modernity is transformed into the science of engineering (Heymann and Wengeroth 2001).

In the *law*, similar attempts have been made. Legal positivism, for many years the dominant theory of law, sought to establish secure criteria for demarcating between law and other related phenomena, like ethics or politics. Significant outcomes of these attempts were Kelsen's *Pure Theory of Law* and H.L.A. Hart's *Rule of Recognition*. According to these theories, there should be some fundamental *fact* about the matter of legal practice that could be used to demarcate it from those other, perhaps more fleeting, fields. In Hart's theory, which may be the most mature outcome of legal positivism, most legal practice comes down to the application of legal rules, which may relatively easily be distinguished from other (non-legal) rules of action. Only in particularly hard cases, where no legal precedence exists, the judge may use his *discretion* in order to decide the outcome. However, on the positivist account "discretion" is not accepted as intrinsic to the legal system; neither are the particular *reasons* upon which the judge may base his decision in hard cases (Dworkin 1977).

In the other main strand of western jurisprudence, *natural law*, in many cases seen as opposed to legal positivism, ethical principles have been sought out that would be valid across distances of time and space. According to a simplistic exposition of this tradition, legitimate law would have to accord with these basic ethical principles. Natural law has been particularly

important in establishing the first modern institutions. Closer to our times, its basically ethical founding, established by thinkers like Pufendorf and Rousseau, has been challenged by legal positivism and the attempt at establishing jurisprudence as a system cleansed of ethical and political considerations (Doublet 1995). However, following the atrocities of world war two, natural law enjoyed a certain renaissance, for instance in authors like Radbruch and Fuller, and, at a later stage, in attempts at giving it a foundation free from metaphysics, as found in (Habermas 1992) or in (Rawls 1971)

Common to the two projects we find the attempt to establish principles of legitimating the constitution. Common to the two, we may also state the commitment to the language of rights, fundamentally those of life and property. However, they differ in the reasons given in support of rights: for the positivist, rights are legitimate because they belong to some legal system (as positivised); within natural law, rights will tend to be seen as *prima facie* duties to be followed, also where there is no legal system to secure them. Hence, the difference between positivism and natural law may for the present purpose be put down to the respective attempts to ground jurisprudence within the two domains of facts (positivism), or values (natural law). Again, we see how the socio-material contract serves the sources of legitimating and demarcate social practices. Like in medicine, these attempts should not be seen as naïve attempts to dispel judgement from practices that obviously are in great need of interpretation and judgement: actual practice will always take place under conditions that do not correspond to the idealised conditions under which the practice of law or medicine actually takes place. However, the tendency of modernity has been to regard (practical) judgement as a rest-category, not of itself capable of establishing basic principles of action:

"The idea that all the practical arts owe a debt to the skills Aristotle calls *phronesis* was not especially welcome to rational-minded thinkers in the modern period. Although, in its Latinized form *prudence*, this term keeps a place in words like *jurisprudence*, its broader implications are largely forgotten" (Toulmin 2003:114).

The out-differentiation of cognition and ethics, nature and culture, alluded to above, was also paralleled by an out-differentiation of aesthetic knowledge. According to Gadamer (1960), the philosophical roots of this separation of aesthetics from the life-worlds are to be found in Kants *Critique of Judgement*. In that work, Kant departs from the understanding of aesthetics, prevalent since antiquity, in which art and beauty were considered legitimate sources of *knowledge*, not to be sharply separated from questions of truth (also scientific), or from

questions of politics or morals. Against this tradition, in which aesthetics could be seen as a theory of perception in general, Kant introduced aesthetics as a *theory of art*. He furthermore appointed the *genius* the legitimate representative of beauty in art and nature (Kant 1968). By this move, Kant completely legitimised the relegation of knowledge from the life-worlds: cognition was the domain of science (physics); ethics was grounded in universal principles of reason, to be sharply distinguished from the influxes of the senses; and now aesthetics, considered as a theory of how we perceive the world, was delegated to the perceptions of that strange and isolated creature: the genius.

When Gadamer re-introduces the Greek conception of aesthetics, then, he does not intend that as a move in a debate about art. His purpose is to *take back*, from science and ethics, some very general categories of thinking and acting; categories that, before modernity, belonged primarily to the humanities: judgement, common sense and a general education. These are all broad categories necessary for what Aristotle termed *phronesis*, practical wisdom, and all necessary for the broad and integrative understanding of specialist practices: "while in a special field the good critic is a specialist, the good critic in general is the man with a general education" (Aristotle 1955:1095a).

We may even, in Gadamer, find support for the more sociological and institutional view sketched above, that as modernity advances, the more general phenomena of good understanding and judgement increasingly have to give way to abstract principles of nature and to the political and legal language of rights. In the face of increasing organisational and epistemic complexity and the accelerated speed of modernisation, abstract principles of thought and action are called upon to replace the domains that previously belonged to judgement:

"Wir leben, wie mir scheint, in einer beständigen Überreizung unseres historisches Bewusstseins. Es ist eine Folge dieser Überreizung und, wie ich zeigen möchte, ein arger Kürzschluss, wenn man angesichts solcher Überschätzung des historischen Wandels sich auf die ewigen Ordnung der Natur berufen wollte und die Natürlichkeit des Menschen zur Legitimation des Gedankens des Naturrechts aufriefe" (Gadamer 1960:4).

If, then, Gadamer had not remained committed to the sciences of the text, and if he had, so to speak, made a 180 degree turn, to observe within the developments of the natural sciences, the parallel relegation of contextual knowledge, he might have been on to a critical understanding of second modernity production and organisation of knowledge even before it took place.

That is, he would have been able to include the material and institutional reconfigurations of the production and distribution of knowledge that has driven modernity beyond its borders.

Second modernity is the stage of modernity in which the drive towards technical and universal solutions to practical problems outpaces the ability of judgement to keep track with developments: "*Die Zweite Moderne erreignet sich, wenn Reflexivität über Reflexion triumphert, wenn nämlich das Reflexivwerden des Modernisierungsprozess die klassischen Selbstbeschreibungen der Moderne obsolet werden lässt*" (Beck and Holzer 2004) [28]. Technical knowledge stands in constant danger of transgressing its own boundaries, without this being acknowledged by the central agents acting to promote that development (Böhle, Bolte et al. 2001) . A similar state of affairs can be expressed by recourse to Sheila Jasanoff's formula, that scientific and social order do not by necessity co-evolve, but are rather in constant need of re-negotiation (Jasanoff 2004). One reason for this being so, is that whereas technical developments themselves can be grasped within the object-languages of science and technology, many of their *consequences* cannot so easily be subsumed under the same categories. Neither does the unintended side-effects of the modern production and distribution of knowledge fit neatly into the legal or ethical language of rights. This is not the least so because of the fundamental agreement of the socio-material contract: insofar as law or politics intrude on the domains of the sciences, they usually do so by respecting the monopoly of those disciplines. As science and technology are not questioned, the language of rights stands in danger of reproducing the ignorance of consequences (social and natural) promoted in the scientific and technical disciplines. The consequences of modernity fall outside of most disciplinary boundaries, and so the issue of making them constitutive of policy-making is still, by and large, an out-standing task (Beck and Holzer 2004).

Let me sum up some of the main arguments of the last sections: the socio-material contract established natural laws and political rights as the main sources of knowledge. In this process, the hermeneutic movement between the general and the particular is sharpened through the material, institutional and intellectual reconfiguration of universality within abstract systems of action. This tendency is further strengthened as modernity progresses and as science and technology are socialised. The decisive threshold to second modernity is crossed when

[28] "Reflexivität", in this context, is to be understood as non-intended consequences of the modern order. The modern order, on the other hand, is primarily given through "reflexion", the basic categories of modern self-description. Hence, there is an increasing tension, but not a downright opposition, between the categories through which we act and think, and the world in which we live.

science and technology, with good help from politics and the economy, transgress their legitimate limits so as to have detrimental (non-intended) consequences to other systems of actions or in the life-worlds. Obviously, this movement of modernity is hard to measure. However, it must be kept in mind that these are (primarily) heuristic considerations: socially and historically situated reflections to be validated through their application to the field of biotechnology in general, and to genomic medicine especially.

The above arguments should now be used to gain an improved methodological overview: By introducing the concept of *judgement* as detrimental to policy and knowledge-based practice in second modernity, I intend to overcome certain short-comings found in many (not all!) studies of science and technology. Latour is a central example: he was used to portray the socio-material contract, but for the drawing of normative conclusions, his conceptual apparatus, i.e. that of "field ontology" remains insufficient. By relying upon aesthetical categories and neglecting the language of the actors involved, he ends up with unstable categories of thought and action. Taking Gadamer as our guide, Latour is speaking about cognitive modernity (science and technology) from the point of view of aesthetic modernity. The one is superimposed on the other. But as we have seen, both of these have been delegated, out of the life-worlds and into abstract systems: science and art.
What remains excluded, then, is the category of judgement as grounded in everyday experience and bodily perception, as well as in social action. Hence, whereas Latour points in the right direction, the language he develops may be at odds with essential issues involved in the analysis of science and technology: what are we going to do? How should knowledge be produced and distributed throughout society?

Obviously, these are big questions, not to be expected solved within any great synthesis. Furthermore, they should be regarded as heuristic and methodological projections for the sake of the following socio-historical analysis. The "conclusion" will have to wait until we have observed some of the central developments on the interface between the laboratory, the clinic, the life-worlds and the law. However, I will try and sum up some of the main points of this last chapter:

1. The scientific object is represented through the scientific community and not through the signifier as commonly presupposed within classical epistemology.

2. Through the socio-material contract specific aspects of reality were delegated to scientific disciplines and professions. The conception of the counterfactual organisers is meant to point towards this delegation of epistemic authority and organisational powers in modernity. Delegation basically takes two forms: either to the material, then through the intermediating representation of science and the scientific community, or to political subjects, and then the delegation takes place through the intermediation of democratic institutions.

3. The above structures must be regarded as dynamic and subject to social and historical change, what Beck terms the *Metawandel* of second modernity. Whereas in first modernity this delegation would function more or less smoothly, in second modernity rationalities tend towards getting muddled up. The principle of functional differentiation is questioned and organisational problems arise that cannot simply be solved through further differentiation (Beck and Bonss 2001).

4. The organisational challenges of second modernity arise not because of some qualitatively new situation, but rather because of an intensification of modernity's founding forces: science, technology, economy and liberal politics come together within new and powerful constellations.

5. One main challenge for regulation is the mediation of increasingly abstract and universal principles of action organisation and the need for judgement in concrete cases. This sharpened conflict between universality and contextuality may issue in increasing, even overwhelming, complexity. One main feature of this is that expert knowledge increasingly comes to be expressed in terms of risk rather than in terms of certainty.

4. The modernisation of medicine

In this chapter I address the modernisation of medicine as 1) a program of research (Claude Bernard), 2) as successful (experimental) action carried out on a broad institutional basis through the manufacture of techno-medical objects. This second perspective is addressed by a description of some central aspects of the therapeutic revolution as exemplified by the work of Paul Ehrlich. What is common to both perspectives, to both Bernard and Ehrlich is the centrality of experimental intervention carried out in the laboratory. They also share in a common commitment to what we may term the positivist ethos of research, in which the *facticity* and the legitimate source of knowledge is positively established and contained within the laboratory before being transferred to other contexts of application. In that respect, the main frame of reference is the clinical application of the knowledge established through experimental intervention. In short: there is to be a 1:1 relationship between experimentally established knowledge and its clinical application. As described by Georges Canguilhem: For Bernard legitimate and successful clinical action is action in accordance with the laws of nature determined through experimental action (Canguilhem 1991).

Although Bernard may have been one of the first to give a coherent articulation of this relationship between experiment and action, it was only first carried out on a broad scale in the following generation of experimental physiologists, during the therapeutic revolution. The findings of experimenters like Louis Pasteur, Robert Koch and Paul Ehrlich did contradict Bernard's image of normality and pathology on one central point: according to Bernard, pathology would arise as a consequence of imbalances in the internal milieu only. Surely the discovery of the actions of micro-organisms did not go well along with this image. But in most other respects there is a remarkable convergence between these figures of early modern medicine, centrally the importance of the close relationship between experiment and application. For the sake of *social action* this is the important aspect.

There is, however, one more aspect to be noted: as the success of the early modern research ethos makes itself manifest, that is not a movement initiated from the laboratory only. The success of Ehrlich did not come from experimental genius alone, he also profited greatly from close connections to the state apparatus and from close ties to industry. Ehrlich's work entered into a social situation in which the chemical industry was becoming a significant factor, what has been described as a "second industrial revolution" (Harwood 2005). Although Bernard, on his side, came to be well aware of the institutional and social implications of his research

program (Coleman 1985), this is one aspect of research that is not articulated in his writings. That stated, Bernard was not alone in ignoring the industrial and economic aspects of research: for many years these were regarded as second or tertiary nature to research, as influences to be avoided (Merton 1973) and never really acknowledged as part of the (first modern) scientific enterprise. This has also made its decisive influence on how we have thought about the past, i.e. about the research practices of central figures like Pasteur, Koch and Ehrlich:

> "Historians and biographers have studied Paul Ehrlich as a biochemist, a medical messiah, and an eccentric. The links with industry of this Nobel Prize-winning pioneer of experimental therapeutics and immunology have, however, been largely neglected. Perhaps this was because commercial involvement was regarded as unseemly by historians, or because those ties were thought to be insignificant in relation to the major contributions Ehrlich made to therapeutic practice and theory. More recently, attitudes have changed…" (Liebenau 1990).

As will be seen later on: in second modernity the situation changes: from exerting a certain *influence* on research, acknowledged and un-acknowledged at the same time, commercial and industrial ties come to make up a *constitutive* force. The ethos of first modernity is decisively challenged and transformed (Wright 1986; Krimsky 2003). Hence, we are dealing with an expansion of modernity, one in which its constituting forces seems to come to interact even more closely and intensely. But that will be a topic of later chapters. For now, I start out by describing the research ethos of Claude Bernard. The main purpose of this, however, is not to describe an ethos as such, but rather to get to the institutional structure in which this ethos was embedded: the organisation of knowing and acting in first modernity.

Claude Bernard and the ethos of research.

The first institutional step towards modern medicine, we may state, came with the Paris clinics in the years following the French revolution. Through a new methodology, the anatomico-pathological, diagnostic abilities were put into action on a wide, institutional scale, finding their ways into clinics all over Europe. Hence, the perception of disease was transformed once and for all, not the least through the introduction of the objectified distinction between *signs* and *symptoms* (Foucault 1973; Ackerknecht 1982; Porter 1997). Although the Paris clinic may have posed an important step on the road towards modern medicine, its diagnostic abilities were not countered by a corresponding capacity in therapeutics. Not least due to the statistical method, elaborated by Pierre Louis, this became

clear. The outcome was a certain therapeutic nihilism on the part of the physicians working in the clinic.

Claude Bernard put this problem down to 1) the methods being used in the clinic, and 2) to the prevailing ontological conception of disease (disease as discrete entities) as defined by Bichat and his colleagues in the Paris clinics.

Concerning the method, which he termed "empiricist", the main problem was its fundamental passivity towards its object. This was a shortcoming which it shared with its predecessor, nosology: both schools were limited to the passive observation of natural phenomena, be it through mere observation at the bedside or through numerous autopsies in the mortuary. The term 'empiricism', which should not be confused with the English school of philosophy of that name, was applied to the physicians of the clinic because of their lack of theoretical guidance. Scientific medicine, Bernard taught, was to be guided by strict physiological rules and not to stumble blindly around in the infinite manifold of experience. All that the 'empiricists' could accomplish, was the collection of facts about the specific diseases and to place them according to type of lesion caused in the specific tissues, organs or body parts. This, however, did not amount to establishing the *causes* of disease; it only meant observation of their effects. Insofar as these were confused for the cause of disease, it was small wonder that therapy didn't work, and that frequently the proper therapeutic measure to be taken was, literally, to abstain from any intervention whatsoever: "Clearly you have never tried doing nothing!", Magendie quoted from (Canguilhem 1994).

In order for medicine to become a science proper, it would have to adopt the methods of the experimental sciences, physics and chemistry. Only through direct intervention with natural phenomena, the scientist could hope to wrest from nature her secrets: "to find truth, men of science need only stand face to face with nature, and in following experimental medicine, question her with the help of more and more perfect means of investigation", (Bernard 1957:221). It follows that the laboratory, and not the clinic, should be the heart and brain of scientific medicine, the fundamental difference being that "The observer accepts phenomena just as nature sets them before him; the experimenter makes them appear under conditions of which he is the master", Bernard quoted from (Coleman 1985).

The ideal for Bernard was to describe physiological phenomena in the physico-chemical language (*ibid*.). In spite of this, he was no blatant reductionist. Although arguing vehemently against vitalist theories as obstacles to scientific progress, he clearly saw that physiology, as the science of living organisms, posed methodological problems on its own terms, which were not met with in the physico-chemical sciences.

In order to deal with this problem, Bernard came up with the conception of *the internal milieu*, by which he was able to combine two seemingly opposing demands. On the one hand, the internal milieu exists on a par with other natural phenomena, and is as such susceptible to physico-chemical analysis. On the other hand, however, the internal milieu is separated from other natural phenomena; it exists for itself, and is therefore responsive to its own internally established norms. The organism responds to challenges put to it by the environment through the regulation of its internal milieu. Therefore, Bernard said, although the processes of the internal milieu are of a physico-chemical nature, these are in turn regulated by way of the physiological processes of the internal milieu, hence pertaining more to the teleological relations between *specific organ functions* than to chemical laws (which are under any circumstance everywhere the same). Therefore, *experimental physiology* is the fundamental discipline of medical science, and not physics or chemistry: "General physiology is the basic biological science towards which all others converge" (Bernard 1957:65).

The normal condition of the internal milieu is one of equilibrium. In this state, the different processes of the body (i.e. nerve system, digestion, metabolism, circulation of the blood…) are co-functioning so as to produce the best possible functioning of the organism as a whole in its exchanges with its environment. The internal milieu is therefore a (teleologically) functioning whole capable of self-regulation, in modern nomenclature termed *homeostasis* (coined by Walter Bradford Cannon in 1929).

Because Bernard thought of nature as homogenous rather than as consisting of qualitatively differing domains he conceived of disease as existing on a continuum with the phenomenon of the healthy organism, the normal, functioning whole. Pathology, he said, is nothing but normality gone awry: it is the quantitative deviation from the normal value of physiological processes: "Every disease has a corresponding normal function of which it is only the disturbed, exaggerated, diminished or obliterated expression", Bernard quoted from (Canguilhem 1991:68). From this he concluded that since medicine was the science of disease

(pathology), and physiology the science of normal function, physiology must be the medical discipline *par excellence*.

Bernard demonstrated his theories through numerous experiments. Among the most significant, we find his treatise on diabetes, published in his *Lectures on Diabetes and Animal Glycogenesis*, in which he argued that diabetes is caused by deviation from the normal amount of sugar contained in the blood (glycemia):

"There is only one glycemia, it is constant, permanent, both during diabetes and outside that morbid state. Only it has degrees: glycemia below 3 to 4 % does not lead to glycosuria; but above that level glycosuria results…It is impossible to perceive the transition from the normal to the pathological state, and no problem shows better than diabetes the intimate fusion of physiology and pathology", quoted from (Canguilhem 1991:70).

Through experiments on dogs, Bernard established that the liver has the ability to synthesise glucose molecules in relative independence from the uptake of glucose from nutrition. Consequently, the ability of the liver (and the pancreas) to regulate the level of sugar in the blood was deduced from this experimentally established fact.

As the above quotation makes clear, the transition from a normal to a pathological level of glycemia can only be established by way of strict quantitative measurement. As has been the case also in other positivist attempts at clearing the fields of science and philosophy of metaphysical content, *subjectivity* also went by the board[29]. In fighting off the ancient, but still prevailing theory of vitalism as unscientific and metaphysical, Bernard found it necessary to dispose of concepts possessive of any experiental value whatsoever.

Thus, "disease" was transformed into "pathology", "health" into "normality" and so on; qualitative connotations belonging as it were to a necessary, but pre-scientific stage on the way towards true physiology.

Also this move was conceived by Bernard in a homogeneous manner: the scientific and quantitative concepts of physiology do not belong to a reality distinct from those of ordinary language. They were so to speak *purified reality*: the complexity of the clinical situation

[29] A modern attempt was that of Rudolf Carnap and the logical positivists program for the social sciences. How was one to treat the so-called "belief-sentences" within a scientific-logical language? The answer, according to Carnap, consisted in ascribing belief-sentences an emotive value only. As such, they were relegated to the non-scientific domain, possessing as it were no cognitive (semantic) value.

reduced to its most basic properties by way of experiments in the laboratory. Thus, we may place the autonomy of the physiological discipline in a specific domain on a continuous scale: as more complex than physics and chemistry (due to the character of the interior milieu), but less complex than clinical science (due to the extractions taking place in the physiological experiment). Curiously (but tactically), the conclusion was drawn that whereas the complexity of the organism could not be reduced to chemistry without loosing sight of the whole, the complexity of *the clinical context* could in a sense be reduced to that of the physiological laboratory. Bernard therefore conceived of the laboratory as the basis, not only for theory-formation, but also for the regulation and ordering of action within the clinical domain. Here was thus not only a theoretical program, but a program of *action* as determined by medical science as well:

"In writing the *Introduction a l'etude de la medecine experimentale,* Claude Bernard set out to assert not only that *efficacious action is the same as science* [the italics are mine, KR], but also, and analogously, that science is identical with the discovery of the laws of phenomenon. On this point his agreement with Comte is total" (Canguilhem 1991:107).

We are reminded of Comtes famous dictum: "savoir pour prevoir, prevoir pour pouvoir". It follows that technology is the application of positively established knowledge. Hence, right action is action in accordance with the laws of natural phenomena[30]. Whereas medicine traditionally had been considered an art, it would have to become a science in order to accomplish this goal:

"Another false opinion, which is pretty well accredited and even professed by great practicing physicians, is expressed in saying that medicine is not destined to become a science, but only an art, and that physicians accordingly should be artists, not men of science" (Bernard 1957), 203.

Natural phenomena, says Bernard, are to be determined through *physiological determinism*:

"Physiological determinism is quite different [from philosophical determinism]. It is the expression of a physical fact. It consists in the principle that each vital phenomenon, like every physical phenomenon, is invariably determined by physicochemical conditions…", Bernard quoted from (Karlsen 2003:30).

Hence, the clinical context takes nothing away from the laws established in the laboratory; it only adds complexity. Formally expressed: natural laws of the laboratory + cultural,

[30] "Phenomenalism" is the view that we can have no perception of ultimate causes and that reality is given us as perceived phenomena only. The classic articulation is given in the philosophy of Kant.

emotional, economical, political + *x* factors equals the total situation of the clinician. The scientifically trained clinician would be the one who knew which of these factors (the natural laws) were therapeutically relevant, and which were not (every additional layer of complexity), and acted accordingly in the concrete case.

As indicated in the above quote, the type of determinism Bernard had in mind was nothing like fatalism, the belief that the course of life is absolutely determined and that there is no such thing as free will. What he meant was roughly this: The laws of nature are directly given to us through intervention with natural phenomena in the laboratory. The primary technique of discovery was, quite consistent with his theory of the normal and the pathological, the destruction, or the temporary halt, of normal functions. By thus manipulating natural phenomena, the goal was the determination of their immediate causes: if you remove the cause for one phenomenon to take place, you also remove the phenomenon. Speaking of the material causes of phenomena, Bernard states that: "These conditions once known, he [the experimenter] can then master the phenomenon; by supplying or not supplying them, he can make the phenomenon appear or disappear at will…thus physiologists gain empire over vital phenomena" (Bernard 1957:75). For instance, Bernard inferred that the liver was of itself capable of producing glucose. He came upon this conclusion by cuttings in the nutrition given to his research animals.

In retrospect, it is clear that Bernard's experimental phenomenalism was an optimistic one, and also, in Canguilhem's sense, an *ideological* one. He held mathematics in low esteem, and he held that the laws of nature must be given to us directly through the experiment: "…in matters physiological one could repeat one's experimental operations and confidently expect that a given phenomenon would return" (Coleman 1985). So even though Bernard's ideas, significantly that of the internal milieu, are of high relevance even in today's biomedicine, here is at least one point of dischord: it is only in very rare cases of pathology (monocausal disease) or in cases of theoretical optimism (Watson: "there is only one science: physics") that we *may* be justified in speaking about determinism in Bernard's sense. Overall, today's models of causation in medicine are *probabilistic* rather than deterministic (Vineis 2000). The disciplines of epidemiology and social medicine would be impossible on a Bernardian account.

In Bernard we find a double set of identifications: pathology is identified with physiology, and physiology is moulded after the ideal of the experimental sciences, physics and chemistry. This last identification was necessary in order for Bernard to carry out the first. Only by *quantifying* the relationship between physiology and pathology, it became possible for him to see the two as identical, and quantification was only possible by excluding every conception of quality from the life sciences (especially as found within the vitalist tradition). Bernard's determinism was thus dependent upon two simultaneous reductions: that of pathology to physiology, and that of quality to quantity, thus "…obeying the spirit of the physical sciences" (Canguilhem 1991:110), as laid down by Laplace, Lavoisier and their likes.

In passing, we should also remark upon the following philosophical point: By insisting upon the experimental character of knowledge, Bernard seemed to be following the Kantian philosophy of restricting the conceptual basis of the discipline to that which could be given phenomenally given only. However, Bernard must have ignored some of the finer points in Kant's philosophy, namely those concerning the continuity of natural laws. For Kant, the *Lex continui in natura* was a necessary logical (transcendental) presupposition of the mind. This rule was *not*, however, to be ascribed to nature itself. For Kant, nature is also strife and discontinuity. It consists of *Reale Oppositionen*, not to be reduced by the mind's inherent dialectical inclinations. Who then, was the greater sceptic: the system-builder par excellence, Immanuel Kant, or the experimentalist Bernard, insisting upon any system, physiological or philosophical, as an obstacle to be done away with in the name of scientific progress? This insistence upon unity and continuity we also find at a later stage in the positivist philosophy of Ernst Mach (Mazumdar 1995).

We therefore state that the goal of Bernard's investigations was *the experimental determination of vital phenomena* (Coleman 1985). As previously stated, the scientific object is to be regarded as constituted by the social organisation of the scientific community around a specific site, the laboratory. Bernard must have realised this: not only was he one of the first to come up with a unified cognitive structure for scientific medicine, he also sought this structure carried out as a social programme. We have already stated the implications that Bernard intended the new physiology to carry with it for clinical action. Between that plan and its realisation there was, however, a gap: how to put the idea into action, into society?

Bernard solved the problem by ascribing to the laboratory a double role: it was to serve simultaneously as the provider of a cognitive structure *and* as the place for training new researchers and clinicians. As Coleman points out, Bernard in his later years went beyond mere theoretical and experimental ambitions: his was clearly also a social project, in which physiology became the prime justification of his overall vision for medicine's role in society:

> "The cognitive elements of experimental physiology were to Bernard a decisive instrument in translating bold explanatory ideals and proposed methods of a science in the making into the worldly needs of laboratory space, financial support, and provision for the training of students, each a function of social organization and together constituting the disciplinary domain par excellence" (*ibid*.).

As described above, Bernard already possessed the cognitive justification necessary for the establishment of physiology as the basic medical science. What he lacked, however, was economical and political support for carrying out his program. Not least due to the strong position of the clinic and the hospital in France; compared to Germany there was no strong laboratory culture to be found. Bernard's experiments were carried out under poor conditions, and for many years he received no support for his work. His results stemmed more from experimental genius than from anything else, being as they were carried out with scarce resources, (*ibid*.).

The physiological laboratory may have taken as its model the chemical laboratory, but as strongly emphasised by Bernard, it posed requirements of its own. Most significantly, the organism was to be studied as a whole in order to determine the immediate causes of vital phenomena, and the laboratory had to be shaped accordingly. Animal experiments were thus of crucial significance. This again required facilities quite specific for the biological/physiological laboratory: keeping a stock of research animals demands space. In addition to chemistry and vivisection, *histology* formed the third methodological pillar of physiology. The new theory of the cell also promised insights into vital mechanisms beyond those of the organs. Hence, *microscopy* was also to be elaborated in order to fulfil the specific requirements of the physiological laboratory.

He was lucky enough to receive the support, financial, intellectual and political, from the minister of public instruction, Victor Duruy. Bernard's efforts coincided with a movement towards national restoration and educational reform starting in the 1860s. One looked

(enviously) towards Germany, where similar reforms had already taken place, and where laboratory research had found a more welcoming environment, not least due to strong support of the universities and their attached scientific institutes (Porter 1997). Of model statuary was the Humboldtian educational reform, by many regarded as the main promoter of German and Preussian economic, political and military progress. Hence, the establishment of the laboratory took place under conditions of strong nationalist impulses, closely mirroring and reproducing the national conflicts taking place between France and Germany/Prussia. As will be seen from the following chapter, a close relationship to the rising nation states was a prominent feature of the expanding experimental medicine.

The therapeutic revolution

> During the seventeenth-century scientific revolution, controversies flared about the proper relations between theory and practice, science and craft, and pure and applied knowledge. The Baconian tradition stressed the marriage of thought and action through experimentation; the scientific society, the private laboratory and other institutions formal and informal put the programme into practice. All these were to have lasting significance for medicine, alongside a further bone of contention: the ethics of the links between the advancement of knowledge and the relief of suffering,
>
> Roy Porter, *The Greatest Benefit to Mankind*.

In this section I describe the first successful large scale application of the experimental ethos of research. I do so in accordance with the previously described modes of reasoning: under a general presupposition of the specificity of micro-organisms, a rational and standardised basis for action was experimentally negotiated and put to use in a clinical context. The success of the undertaking for the following organisation of biomedicine can hardly be underestimated: through the organiser of specificity organisational powers were effectively delegated to powerful therapeutic techno-medical objects. These were also the early days of industrial pharmacology and the beginnings of the tightened relation between the state and science as carried out through experimental action, state intervention and a growing health care sector.

Before we get started, I should also comment upon some methodological choices of the following section. In a relative contradistinction to the later account of the genetics, I have relied upon works within the history of ideas rather than upon the approaches taken within the science studies literature. Centrally, I have used (Silverstein 1989; Mazumdar 1995; Tauber 1997; Silverstein 2002). These are all central works within the emerging discipline of the history of immunology, and they complement each other nicely by focusing upon the same period of time but from the perspectives of different experimentalists and disciplines (i.e. Silverstein focus particularly on Ehrlich the biochemist, Mazumdar on the physical chemistry of Pauling, and Tauber on Metchnikoff's biological approach). However, they do not particularly concern themselves with the institutional dimensions. I have tried to remedy this by introducing some other authors emphasising the institutional aspects. I do indeed take the therapeutic revolution to be something of a historical and social fact, and as such I may be involving myself in the writing of "wig history". However, it should be kept in mind that this is not a work in history, but rather a socio-philosophical reconstruction of some institutional and epistemic dimensions taken to make up central parts of the *Wirkungsgeschichte* of experimental and clinical interactions. I precede more from the presupposition that this constellation is central to understanding the present, than from a historical description trying to establish or explain that state of affairs.

The work of Bernard and his fellow German pathologists (like Virchov and Muller), operating between 1830 and 1880, had been devoted to the search for the underlying functions of vital and pathological phenomena. As such, they belonged to what Pauline Mazumdar has termed "the Unitarians" (Mazumdar 1995). Nature was projected as continuous and homologous, revealed by the experimenter through the determination of vital phenomena. According to this view, the seeming manifoldness of natural phenomena was simply an expression of the underlying *unity* of nature.

In contradistinction to the Unitarian view, the next generation of experimentalists would be dominated by the search for *specificity*: Pasteur in France, Koch in Germany, a dominance which was to last throughout the first half of the 20th century. The stereochemical reaction (to be explained), as conceived by Paul Ehrlich, permitted of no cross-reactions between chemically different substances or between different sera or anti-sera. This conception was

described as teleological: the *Raison d'Etre* of the antibody was to react with the specific antigen with which it corresponded.

The serological approach to immunity

Hence, even though the next generation of experimental physiologists were to continue and strengthen the development of the laboratory as knowledge base, they also, on significant points, deviated from Bernard's program. First, *chemistry* more or less replaced the conception of vital phenomena as the dominant physiological theory. This was not least due to the successes of great experimentalists such as Louis Pasteur and Robert Koch, working in the field of bacteriology. In providing effective vaccinations and therapies against a great number of infective diseases such as gonorrhea (1879), malaria (1880), tuberculosis (1882), cholera (1883), diphtheria, tetanus (1884), and rabies (1885), they launched what would become a revolution in therapeutics (Tauber 1997). Chemistry gained a momentum that would make it the basic discipline within immunological research right up until the 1950s, (Silverstein 1989)[31]. This also meant that bacteriology and immunology in the first half of the 20th century by and large rejected significant developments within biology: 1) the Darwinian idea of the transformation of one species into another due to adaptation to the environment; 2) the cellular pathology of Rudolv Virchov, according to which disease was not the result of an imbalance of the humours (as claimed through 20 centuries by the Galenic tradition), but rather of malfunctioning cell formation; 3) Elie Metchnikoff's phagocyte theory of immunity, which owed much to both Darwin and Virchov (Tauber 1997). Thus, Arthur Silverstein writes of the reception given to the immunological branch of the new biology that

> "…the cellular theory of immunity advanced by Elie Metchnikoff in 1884 did not constitute just one further acceptable step in a well-established tradition; rather it represented a significant component of a conceptual revolution with which contemporary science had not yet fully learned to cope" (Silverstein 1989:41).

As with the Paris clinicians, the ontological pluralism (the notion of discrete entities) taken up by the serologists was not mirrored by a corresponding *epistemological* pluralism. On the contrary: the stronger the connection to physico-chemical methodology, the stronger the exclusion of other languages. In this way, strong presuppositions about the nature of things were also made, namely through the "thesis of the applicability of the laws of the inanimate world to vital phenomena" (Moulin 1988). Through this adhesion to the language and

[31] In accordance with Silverstein's exposition this immunological tradition, most powerfully represented by Robert Koch and Paul Ehrlich, is hereafter termed the *serological* approach to immune phenomena.

methodology of chemistry, Robert Koch and Paul Ehrlich went a long way in establishing a scientific basis for the understanding of a wide range of diseases as well as for effective clinical interventions. The close connections to the chemical industry of the times would also secure a fast industrial response as soon as a proper methodology for standardising anti-toxins was established.

Robert Koch

Parallel to Louis Pasteur in France, Robert Koch made important discoveries concerning the connections between specific bacteria and specific diseases. His scientific break-through came with his demonstration of the life-cycle of the Anthrax-bacillus, performed at the University of Breslau in 1876 in front of a number of highly influential scientists, among them the botanist Ferdinand Cohn and the pathologist Julius Conheim. In short, what Koch proved was the conditions under which the reproductive organs of the bacteria, the spores, took place and how the spores would next develop into bacteria. He also demonstrated the highly *specific* relationship of the spores and the bacteria to the Anthrax disease itself. The demonstration was revolutionising and highly effective, not least because it defined and proved the specificity of bacteria in front of a highly receptive and important audience, (Mazumdar 1995). A central dogma of Koch's, which was adopted and developed by Paul Ehrlich in the area of immunology, went as follows: "A distinct bacteric form corresponds…to each disease, and this form always remains the same" Koch quoted from (*ibid*., 66).

Louis Pasteur had already developed vaccines against both Anthrax and Rabies. But a thorough and methodological explanation and identification of the causal agents, the micro-organisms, had not been given until the time of Koch's demonstration, and so one lacked the insight needed to develop effective therapeutic regimes (Pasteur grouped and named the micro-organisms according to the disease caused, and disregarded the morphological specifics of the micro-organisms). Koch opened up for categorising bacteria in the same way as was done with species within botany. Further discoveries followed, significantly of the tubercle and the cholera bacilli. Until Koch's demonstrations, conceptual and experimental uncertainty had reigned in botany as well as in bacteriology as to the status of both mono-cellular organisms and bacteria. Following the tradition from Aristotle and Linneaus one wished to classify micro-organisms as to species, genus etc. But this was problematic because of the size of the task: technological innovations were needed in order to be able to determine the

morphology of micro-organisms. Robert Koch clearly grasped this problem, and he pioneered the use of contemporary technological innovations:

First, *microscopy* was improved. The development of the art and science of microscopy was strongly represented in Germany, not least due to the works of Ernst Abbe, who developed new illumination techniques for the company of Carl Zeiss. Second, *staining techniques* were brought from the chemical industry (anilin) and used for staining bacteria in order to differentiate between them. Third, Koch changed the *media* used to cultivate bacterial cultures. Pasteur had deployed liquid media for this purpose. Improvements of microscopy techniques discovered impurities and distortions of the cultures by the liquid media, and Koch therefore developed techniques using dry media. For this purpose he deployed sliced potatoes and *agar-agar*, an extract from Japanese sea-weed. Finally, whereas botanists and cell-biologists traditionally had *drawn* micro-organisms, Koch combined microscopy with *photography*, the result being great improvements of precision. The visual fixation of chemico-organic processes at specific stages furthered the view of micro-organisms as discrete entities:

> "Koch's procedure was to smear the bacteria out on a microscopic slide, to separate them, to dry the smear to keep the organisms still for observation, to stain them with the aniline dyes to make their appearance clearer, and finally to photograph them instead of making drawings" (Mazumdar 1995:63).

As already remarked upon, Koch's approach to the study of micro-organisms received a welcoming reception within a well-established school of research at the University of Breslau:

> "Koch's visual technology and his emphasis on morphology linked up perfectly with Cohn's traditional botany to form a style that was taken up by the whole Koch school and its later descendants and the goal of which was to arrive at an accurate subdivision of species" (*ibid.*, 102).

The Germans also possessed important competitive edges through other industrial and technical innovations. Chronologically, but also methodologically and conceptually prior, was the establishment by the organic chemist Justus von Liebig of his institute in Giessen, where he established one of the most important educational and research facilities of the day. Liebig gained worldwide recognition for his work with the organic and inorganic chemistry. Together with his colleague Friedrich Wöhler, he performed chemical investigations of nutrition and metabolism, thus establishing the foundations of what was to become *biochemistry*. Liebig and Wöhler educated hordes of students in the application of physico-chemical analysis to the living body, thereby promoting scientific materialism as the leading

ideology of research, and furthering pharmacology and physiology as basic medical disciplines (Porter 1997; Fruton 1999).

Closely connected: after 1850 the chemical industry in Germany boomed. Starting out mainly as manufacturers of dyes (particularly *aniline*), by the end of the nineteenth century many of the same skills and techniques were also applied to the manufacturing of drugs (Weatherall 1996). Close connections developed between the chemical industry and research institutes, in which it may fairly be stated that the industrial was just as much a precondition of the scientific developments taking place as the other way round (Pickering 2005). These powerful constellations secured growth bypassing that of Britain and France and lasting up until the present day. Large-scale companies like BASF, Höechst and Farbwerke Cassella were all parts of this development. The building of industry and research laboratories formed an important part of the growing nationalist movement in Germany. Following the rise of the German states in the 1840s and, after the Franco-Prussian war, their unification, there existed in Germany a particularly close relationship between industrial leaders, government officials and university professors (Fruton 1999). As stated by William Coleman:

"By the late 1860s, science and medicine across Europe had become a convenient tool for popular statecraft, not to mention petty nationalism; national power and prestige, especially in France and Germany, were finding a new measure. Some traced the dramatic ascent of Prussian military power and German economic activity to the widespread encouragement of science in these lands" (Coleman 1985).

Hence, there definitely existed a favourable climate, political and industrial, for the application of experimental chemistry to physiological and pathological phenomena. But the scientific approach was also being forwarded in another, more medically related context, namely that of *hygiene*, in which Koch was to play a particularly central role.

In 1880, Koch was appointed advisor of *The Imperial Bureau of Health* in Berlin. Up until that time, hygienic practice in Germany had been headed by Max von Pettenkofer, professor at and founder of the *Institute of Hygiene* in Munich. Pettenkofer took his methods from the British sanitary movement, emphasising water supply, sewerage, ventilation as well as the purification of the city milieu and the soil from fermenting and putrefying substances, (Mazumdar 1995). The methods deployed were based on the collection of data and statistics, and the data collected were used as basis for legislation and intervention on a *local* level. From an etiological point of view, the justificatory theory of Pettenkofer was that of the old

miasma theory, the idea being that different diseases stem from fermentation and putrefaction of impure substances residing in the soil. As in France, etiologies based on the theory of miasmas was thus limited to local circumstances (Foucault 1973). Pettenkofer's hygienic methods were based on local statistics and aiming for interventions on a corresponding level. Hence, Pettenkofer also opposed legislation from the recently established central government, an attitude that was welcomed by mercantile and liberal centres such as Hamburg (Mazumdar 1995).

From his position in Berlin, Koch soon came to dominate the hygienic movement. Following important scientific discoveries of the Tubercle bacillus and the Cholera bacillus, his popularity rose throughout Germany, and he was duly recognised also by the state. He soon replaced Pettenkofer as the leading figure of the Cholera Comission, and he was given his own institute in 1891 (The Institute for Infectious Disease), and he was steadily promoted through the military system as well as through the civil system. As already remarked upon, there existed a particularly close connection between the military system and the state, and Koch profited from his good connections in both ranks. Many of his students were closely connected to the Sanitary Corps, and many were trained at the military medical school, (*ibid*.).

As seen from the description of some of Koch's central discoveries, his success by no means came unwarranted. He may rightly be termed the father of scientific bacteriology[32], and his methods were central to the discovery of a great number of diseases: diphtheria, typhoid, gonorrhoea, pneumonia, undulant fever, meningitis, plague, leprosy, tetanus, syphilis and whooping cough as well as other streptococcal and staphylococcal infections (Porter 1997). Still, there is a rather long way from the laboratory to the realms of legislation, state intervention, and to concrete hygienic measures undertaken on a broad, social scale. For instance, the modern heir to hygiene, social medicine, may in its methods be just as resembling of Pettenkofer's statistical methods as of Koch's bacteriology. Thus, it seems that additional factors were required for Koch's success. Pauline Mazumdar remarks that

"Koch's cholera programme was the opposite of Pettenkofer's in every respect. He pushed for border controls, quarantines, boiled water, strong state intervention, and health legislation on a national scale. The civil authorities supported Koch to the hilt in these movements…Koch's sudden and complete eclipse of Pettenkofer at the Bureau of Health may have been due less to his 'correct' theory of disease

[32] For instance, Koch's postulates, formulated to prove the causation of a given disease by a specific agent, are still in use, (Dorlands Illustrated Medical Dictionary).

transmission, than to its consonance with the desire of the central government to impose itself upon its constituent states" (Mazumdar 1995:85).

Although Koch came a long way in establishing a convincing and efficient theory of bacterial specificity as well as a powerful social network through which his ideas could be spread, it would take the interventions of Paul Ehrlich to establish a scientific basis capable of standardisation on an industrial scale. I now turn to a description of some of the events that went to make up, for the first time, a global basis for therapeutic intervention.

Paul Ehrlich and the early days of immunology

> Therapy, the most important branch of medicine, has from the outset developed on empirical grounds, in which more accidental or incidental observations on cures, be it in man or animal, led to the approach to practical use. Thus it was that the greatest majority of therapeutic substances have been attained, such as quinine, opium, and mercury. Only in recent times, especially with the progress in pure chemistry, have changes been made in this. One strives for the time when insight into the *essence* of drugs is attained, and to decide the question in the first instance of the relationship between the constitution of these substances and their *therapeutic* action. Justifying this approach was especially the more accurate research of the alkaloids, which showed that the great number of these variously active substances [have] a common nucleus similar to pyridine, to which side-groups connects as the carriers of physiological activity. This knowledge must necessarily lead to the desired goal of the synthesis of new drugs…it will in fact be possible by means of certain combinations to eliminate nearby damaging activity without prejudicing the curative potential,
> Paul Ehrlich, 1891, quoted from (Silverstein 2002).

Through the history of modern science, only a few persons may have been able of matching such a strong formulation of the positivist research ethos with corresponding successful actions as was Paul Ehrlich. Drawing a line from Claude Bernard up until present articulations of the same 'ethos-paradigm' of research, Paul Ehrlich may be seen as a privileged transitional figure, one in which normative justification and practice came together to a remarkable degree[33]. While not aiming to subtract anything from the unquestionable genius of

[33] Taking as our clue Tranøy's distinctions, I here refer to internal as well as external normative justification.

Ehrlich, it should nevertheless be clear that the successes of early immunology were not due to one person alone, but also to an extremely creative environment *and* favourable historical and institutional settings. Ehrlich was by no means the only person responsible for the remarkable developments that took place within immunology specifically, or medicine generally, in this period. Still, as remarked by (Silverstein 1989; Tauber 1997; Silverstein 2002), he became the leading figure in the therapeutic revolution that took place in bacteriology and immunology around the turn of the century. Ehrlich the person, then, should not be regarded as the efficient cause in the developments that took place, but rather as one talented person ending up in the privileged position of articulating and putting into experimental practice something very close to the general *episteme* of his time.

In 1890 Emil von Behring and Shibasaburo Kitasato, working in Koch's Hygienic Institute, discovered that resistance towards diphtheria and tetanus is due to the creation of antitoxins against toxins created by the bacteria. Here was a possible explanation for immunisation against anthrax and rabies, as demonstrated by Koch and Pasteur, which also promised fast gains in therapeutic outcome. As it turned out, immune serum would not only protect the host (active immunity), it could also serve to immunize other animals through the transfer of immune serum (passive immunity), or even to cure infected animals were disease was not too far advanced.

As described by Silverstein, Mazumdar and Tauber, the discovery of serum-mediated immunity would not only establish immunology as a scientific discipline, it would also direct research for the following half century in a chemically oriented direction. As mentioned above, this ensured that the biological approach 'proper', notably as promoted by Elie Metchnikoff, would not regain its legitimacy until the biological revolution of the 1950s. In what follows, I will try to reconstruct *some* of the theoretical and experimental results of this orientation, the clinical contexts into which they entered, and some wider institutional preconditions for the successes of the serological paradigm. Theoretically, it appears that the presuppositions that would grant the serological paradigm dominance for half a century would eventually also lead to its demise. I will return to that issue towards the end of this chapter.

At the time of von Behring's and Kitasato's discovery, it was widely held that all infectious diseases develop due to toxins liberated from pathogenic organisms. Highly significant was the discovery of Roux and Yersin in 1888 of the diphtheria toxin, proving that the disease was

caused by the toxin and not by the bacteria itself. The discovery was soon followed by similar demonstrations with respect to tetanus (Kitasato) and tuberculin (Koch) (Silverstein 2002). Hence, it was inferred that the road to therapeutics lay in the cultivation and administration of the corresponding anti-toxin. Some time into the 1890s, rumours of the isolation of an effective agent against diphtheria was spreading, raising expectations in medical circles extending far beyond the borders of Germany. Furthermore, several chemical companies had taken an active interest in the commercial potential of von Behring's discovery (Liebenau 1990). There remained, however, serious obstacles to the wide-spread transfer of the anti-sera:

First, the nature of the protective body was poorly understood. von Behring and Kitasato described it in vague terms, like 'sera' or even 'forces'. As late as 1906, Louis Hallion classified the question of the existence of antibodies as 'a metaphysical one' (Cambrioso, Jacobi et al. 1993). Paul Ehrlich, though, applied the concept of the antibody already in 1891, although he used it in a mainly non-technical sense. The bacteriologist Hans Buchner was the first to try to give a definite meaning to the concept, his suggestion being that the antitoxin/antibody was a product of the bacteria itself, and that '…they may even be different modifications of one and the same substance', Buchner quoted from (Silverstein 1989:61-62). According to Silverstein, this (in retrospect) simplistic solution is highly understandable since, at the time, "…nothing was known about the chemical nature of toxins or antitoxins and little was known about the chemistry of biological macromolecules in general", (*ibid.*, 62).

Second, there were serious problems with the *quantification* of anti-sera. The first attempts at clinical application were with the treatment of diphtheria in children. These attempts failed, largely due to problems with the dosage of antiserum: no method existed for assaying the strength (the "titer") of the serum, and the outcome varied accordingly. In most cases, the serum used was too weak to have any effect whatsoever. The Höechst Company, with whom von Behring had made a contract about the manufacture and sale of anti-diphtheria serum threatened to withdraw from the contract (*ibid*.).

In sum, at least four basic questions had to be dealt with: 1) what is an antibody? 2) How does it originate? 3) What is the nature of the interaction between antigen and antibody? 4) How can anti-sera be titered so as to standardise it for effective clinical use?

In 1891, Paul Ehrlich was appointed at Robert Koch's Institute for Infectious Diseases. By then, he had already been working for Koch at the unit for the clinical study of tuberculosis at the Moabit Hospital in Berlin (containing some 150 beds) (Silverstein 2002). Having already performed successful demonstrations with the titration of the plant toxins *abrin* and *ricin*, he was now urged on by von Behring, the Höechst Company and by Koch himself, to apply his abilities to the solution of the problem of standardisation of anti-diphtheria serum. Building upon earlier experiments of his, it was during this work that Ehrlich would give his own, highly imaginative, solutions to the other three questions posed above. Significantly, he came up with his famous 'receptor theory', or 'side-chain theory', of the antigen-antibody interaction. Continuing the tradition from Koch, viewing bacteria as highly specific organisms, Ehrlich came up with the conclusion that also the antigen/antibody-interaction was characterised by absolute specificity. Antigens and antibodies were discrete entities.

I start out by giving a short description of Ehrlich's works with abrin and ricin, before I turn to the application of the techniques thereby developed to the more complex case of anti-diphtheria serum. Following that, some attention will be paid to early theorisation about immune reactions in general.

In his experiments with plant toxins[34], Ehrlich had found that research animals would withstand very high doses of toxin, as long as they were administrated in gradually increasing doses instead of one single dose. Correspondingly, the amount of anti-toxin contained in the blood serum of the research animal, would be much higher. This was in itself an important discovery, insofar as it would facilitate the production of high-titrate dosages of antitoxin that could next be separated out from the blood of the animal, packaged and administered to a different animal or a person. But it also made way for the important insight that immunity was a highly dynamic phenomenon, and that the development of tolerance would have to be studied as such.

The first challenge lay in the quantification of the toxin's titration curve, so as to facilitate its reproducibility. Ehrlich started out by finding the amount of toxin necessary to kill one research animal. He found that 0,035 mg of ricin would suffice to kill one white mouse, the

[34] Plant toxins were used because they, in contradistinction to toxins produced by bacteria, already existed in pure state and as commercially available (Silverstein 2002)

endpoint of the assay being death within 5 to 6 days. He termed this amount the median lethal dose (MLD), thereby establishing this as the basic unit of toxicity.

Once the titration curve of ricin was established Ehrlich moved on to the quantification of the corresponding degrees of immunity (*Immunitätsgraden*) found in the test animals. This was measured as the greatest number of lethal doses (MLDs) that the animal could withstand following the gradual inducement of immunity through injection of increasingly higher doses of toxin. By the combined oral and subcutaneous introduction of toxins into the research animals, he was able to reach a degree of immunological tolerance of 400 MLDs by the end of the third week, whereas he would never be able to exceed a degree of 1000 MLDs.

As the goal of the experiments on anti-diphtheria serum was of a highly practical nature -that of standardising antiserum for the treatment of diphtheria in humans, Ehrlich and his co-workers set about to establish even more accurate measures for the antitoxin. The main problem with von Behring's approach, they inferred, was that it was based upon the *in vivo* reactions of the research animals. von Behring had proceeded by the injection of a certain amount of antiserum into the animal, thereafter testing it for the amount of toxin it would protect against. But this approach yielded highly varying results, as no two research animals (in this case guinea pigs) would withstand the exact same amount of toxin. Hence, Ehrlich and his assistants turned to *in vitro* experiments, as these would not be that influenced by individual variations[35]. They started out by mixing differing amounts of antiserum with a pre-established standard amount of toxin (taken from von Behring). Following this, the mixture was injected into the research animals[36] to test for residing toxicity. In the end, the results were stable enough to define one 'Immunization Unit' (IE) as the mount of antiserum required to neutralize 1.0 cc of Behrings standard toxin, (*ibid*.).

Having thus established a standard unit for anti-diphtheria titration, the antiserum was tested clinically, this time with highly successful results: in trials carried out in different Berlin hospitals, 168 out of 220 children recovered after the treatment. A major reason for the remaining death rate was the late onset of treatment in these cases. Where treatment was

[35] In a later study, they would further demonstrate the superiority of the *in vitro* approach to that of the *in vivo*. The endpoint of the toxin/antitoxin reaction, defined as the difference between a severe reaction and no reaction at all, would vary within a 20 % limit *in vitro*, whereas the same limit would be 150 % *in vivo* (Silverstein 2002).
[36] Ehrlich used goats instead of guinea pigs, as he found that they produced higher amounts of diphtheria antitoxin.

given on the first day of symptoms, the survival rate was 100 %. The main conclusions of the clinical trials was that treatment was to be commenced as early as possible, that high titer antisera be employed, and that it should be administered gradually and in progressively stronger doses. In Silverstein's words, Ehrlich and his assistants succeeded "for the first time [to] provide serotherapy with a rational basis", thereby providing "a *vade mecum* for the clinician facing an outbreak of diphtheria", (*ibid*., 44).

These outstanding results soon were brought to the attention of both clinicians as well as the Prussian Ministry of Education. The minister, Friedrich Althoff, instantly made Ehrlich head of the Royal Institute for Serum Testing and Serum Research in Berlin-Steglitz, where he continued the work on the nature of immunity (*ibid*.). However, work at the institute was not restricted to the purely theoretical and experimental. A range of products had already been marketed in Germany and abroad. Out of concern that these be distributed uncritically, the German Ministry of Health had imposed regulations as early as in 1894, restricting the sale to authorised apothecaries and on the condition of the sera having been prescribed by a medical doctor (Liebenau 1990). These procedures, however, presupposed some authorising agency, and so in 1895 the Control Station for Diphteria Antitoxin was established in direct connection to Robert Koch's Institute for Infectious Diseases. However, the pressure on the facility, not least due to large-scale production initiated by companies such as Hoechst, Schering and Merck, demanded that the testing functions of the Control Station be expanded. Thus it was that the Steglitz Institute was created and Ehrlich appointed its leader (*ibid*.).

During the Steglitz period certain companies emerged as better cooperative partners than others. Among German companies, Hoechst and Schering had taken a more profound interest in Ehrlich's work, and methods of measurement and standardisation were developed in close connection with these companies. Ehrlich himself was not content with practices in many other companies, and it seemed that lack of attention to procedure and measurement issued in lowered safety and a lack of purity and consistency in their products. This was confirmed in 1896 when *The Lancet* tested the stability and potency of products from a number of companies from Germany, England, France, Belgium and Switzerland. Huge varieties were discovered, but the products developed by Hoechst and Schering in cooperation with the Stiglitz Institute came out as superior. Constellations emerged in which science, regulatory apparatus and parts of the chemical and pharmaceutical industry would mutually strengthen each others positions:

"The procedures which he [Ehrlich] outlined were officially confirmed by an order from Althoff in 1897 and the methods, developed in close co-operation with Hoechst and Schering, were applicable to the rest of the industry. In order to meet the standards, moreover, manufacturers were to obtain fresh supplies of standard toxins from Ehrlich's laboratory about every three weeks. Such dependence worked distinctly in favour of those who had produced antitoxins early, and particularly for Hoechst" (*ibid*.).

From practice to theory

In the years between 1896 and 1899 Ehrlich continued work on the problem of standardisation of antisera. Compared to the stability of ricin and abrin the experiments with diphtheria antitoxin still left something to be desired. As we have seen they had been based upon a unit of toxicity that was taken from von Behring. This posed several problems:

First, von Behring's unity of toxicity was itself unstable: it would contain varying degrees of other substances that interfered with the assay. In addition to this, it was contained in a solution of glycerine, which was supposed to stabilise it. Ehrlich, however, felt uncertain as to the function of glycerine, and he searched for a way of containing the serum without the addition of solutions. By avoiding all contact with light, water, oxygen and heat, he sought to establish a standard serum that would remain stable. The standard serum would then be put into tubes and distributed globally.

Second, the old 'standard' had been based upon the degree of inflammation caused in living animals, which proved a too uncertain measure. As already described, Ehrlich would replace this approach by *in vitro* measurements: he set the endpoint of the assay to be death within 4 to 5 days of a standard 250 g guinea pig. He then defined one immunity unit as the amount of antitoxin required to neutralise 100 lethal doses of toxin. In this manner, he paved the way for what was to become 'the first biological standardization' (Mazumdar 1974).

Having thus established a standard for the titration of diphtheria antitoxin, he used it to make measurements of different standard solutions of antisera, samples being taken from different laboratories in Germany and abroad. The measurements were based upon two set values: L_0, which was the amount of (new) toxin neutralised by one unit of standard antisera, and L_+, which was the amount of (new) toxin required to leave one lethal dose of toxin after neutralisation by one unit of (standard) antisera. *A priori*, this should mean that $L_+ - L_0$ would always leave one lethal dose of toxin. But this never turned out to be the case with any of the solutions that Ehrlich tested. The difference between L_+ and L_0 always turned out as higher

than one, and the difference increased with time: among 11 samples tested, the resulting differences varied between 1.7 and 22 lethal doses (Silverstein 2002) (Mazumdar 1974).

The *practical* solution to this problem would be to continuously supply manufacturers with fresh antisera from Ehrlich's Steglitz Institute, and to make sure that it was not unnecessarily exposed to light, air or heat so that the standard serum would not deteriorate (Liebenau 1990). But Ehrlich also took an active interest in the theoretical foundations of immune reactions, and one department at the institute was particularly devoted to this task. In order to explain the perplexing results, Ehrlich had to resort to a degree of speculation and theorising that had not been central to his experimental works so far.

It was concrete, experimental problems, namely those of giving an adequate explanation of the action of immune serum, which instigated Ehrlich's more theoretical speculations about the antigen/antibody reaction. When he came up with a solution, and, eventually, a theoretical explanation of it, his side-chain theory, it was based upon views about biochemical reactions that had been part of his experimental works for years, but never articulated into a coherent theory. As remarked by several commentators, there was a red thread running through most of his works, namely the chemical approach to biological phenomena. Ehrlich himself wrote that

"Anybody who considers the diverse activities which are carried out by each individual cell, cannot but agree with Pflüger's view that living protoplasm must represent a giant molecule. Everything – specific vital activity, reproduction, assimilation, growth, multiplication, perception, thought, will – is the work of the cell substance…the expression of a certain chemical organisation…" Ehrlich quoted from (Mazumdar 1974).

From structure to function

Ehrlich's approach to biological phenomena had always been from the point of view of 'pure chemistry'. He would consequently think of the relationship between chemical and biological substances in terms of discrete molecular entities, as connecting through absolutely specific properties and as forming non-reversible complementary structures (Silverstein 2002). In other words, he held that specific chemicals were capable of connecting to specific types of tissue or cell, and only to these (Mazumdar 1995). A telling example of this approach would be his early works with the staining of tissues and white blood cells (erythrocytes). His inaugural dissertation had been on the staining of tissues using aniline dyes from the coal tar industry. In this work, he claimed that the specificity of the reaction of tissue with the dyes

was due to a particular dichotomous structure of the (dyeing) molecule: it would have to contain one group for binding to the tissue, and one for supplying the colour. This last group he termed the *chromophore* group. The binding group he conceived of as a salt, hence as being either basic or acidic.

In a way reminiscent of Koch's classification of disease according to the specific micro-organism that had caused it, Ehrlich now applied his techniques of staining in order to define and classify leucocytes. Even though these blood cells could not be classified as species in the ordinary, natural historical or biological sense of the word, Ehrlich would nevertheless treat them as if they were. The classification of blood cells was performed according to a previous classification of the chemical properties of the dyes; these could be *basic*, *acidic* or *neutral*. The white blood cells were classified into five different groups. This was performed according to different granules found in the protoplasm of the cell, which could be differentiated according to their reactivity with the specific dyes. Hence, three out of five groups of leucocytes were named after the chemical properties of dye-stuffs: *Neutrophiles* react with a neutral solution, *Basophils* with a basic solution and *Eosinophils* with the acidic solution *Eosin*. Therefore, ordinary classificatory criteria from natural history and biology were neglected; organs of reproduction were of course not an alternative. The morphology of the cells was, however. But also this perspective was subordinated to chemical structure, as it turned out that morphologically identical blood cells showed a habitus that would differ according to chemical properties (Mazumdar 1995).

Turning to the problem of standardising diphtheria antisera described above, Ehrlich deployed many of the same insights. The initial problem was as follows: he had defined two limit values: L_0 and L_+, where L_0 was taken to signify the number of lethal doses of (new) toxin that would be neutralised by one unit of standard antitoxin, and L_+ was the amount of (new) toxin required to leave one lethal dose of toxin after neutralisation by one unit of (standard) antiserum. Logically, this should always leave him with one unit of toxin after subtracting L_0 from L_+. As already described, this never turned out to be the case, as the toxicity decreased with time.

Also in this case, Ehrlich turned to a dichotomous explanation based upon absolute (chemical) specificity. In a way similar to that of the analysis of the blood cells and of the dye/tissue interaction, he surmised that the antigen molecule would have to consist of two different

atomic groups, each with its distinct function. One, called the *haptophore* group, would be responsible for connecting to the antibody (i.e. its affinity for the antibody), whereas the other, the *toxophore* group, would be responsible for the antigen's toxicity.

Now, the L_0 value would be an expression of the *affinity* of the antigen to its antibody, and this value would remain stable over time. This meant that the antigen would still be neutralised by the antibody, but it would not be toxic. The L_+ value, on the other hand, would be the expression of the toxicity of the antigen, and this appeared to change with time and temperature. In keeping with the school of absolute specificity (cf. Mazumdar, 1995), Ehrlich would not accept that a quantitative down-graduation (*Abstufung*) took place within the same atomic group. Instead, the conclusion was drawn that toxicity declined as a result of the unstable toxin group changing into a *toxoid*; a discrete, non-toxic group. Hence, whereas the affinity of the toxin remained stable, its toxicity did not. This theory was to some degree supported by experimental findings with guinea pigs: by the injection of old toxin into guinea-pigs, the lethal effect would not occur. It would, however, cause paralysis in the test-animal. This was taken as evidence that a qualitative leap had taken place along with the break-down of the toxin, turning it into an altogether different substance (*ibid.*, 117).

Ehrlich also made further subdivisions among the toxins, consisting of proto-, deutero-, and trito-toxins, according to the respective affinities for the antitoxin. These were further divided into two types, *alpha* and *beta*. The *toxoids* he divided into pro-, and syn- toxoids. The idea was next that the toxins with the highest degree of affinity for the antitoxin would be the first to enter the chemical interaction, next to be followed by the second strongest, and so on. In this manner, Ehrlich's audience was presented with a picture of the toxin as a preparation consisting of several, discrete substances with varying degrees of affinity and toxicity, (Silverstein 2002).

Alas: When the molecule's chemical structure changed, so did its function. This extensive differentiation according to structural premises was more a logical consequence of Ehrlich's theory of absolute specificity than it was of experimental findings. According to the *law of definite proportions* two substances will fix each other only if they possess absolute structural

compatibility[37]. Only in this case would we have a chemical reaction proper. The approach was termed 'stereochemical' and Ehrlich would also frequently use the metaphor (borrowed from Emil Fischer) that antigen and antibody would have to fit like 'lock and key' in order to interact (Mazumdar 1995).

This theoretical approach had at least one great advantage: it would serve as a possible explanation of the existence of immunological specificity. Specificity, it seemed to Ehrlich, could be explained by the fact that certain antigens would react with certain antibodies and not with others, as for instance seen in how they would seek *that* specific antibody, existing in *that* specific site in the organism. For instance, tetanus toxin would connect to the central nervous system and not some other visceral organ (Silverstein 2002), 80.

But the 'solution', based on the assumption of absolute specificity of antigen/antibody met with stark opposition, and the debate over the nature of the reaction would dominate immunological practice up to the replacement of serology by cellular immunological theory (Silverstein 1989). The debate was sparked in 1897, when Ehrlich presented a paper on the standardisation of antidiphteria serum, in which he also touched upon the theoretical question of the origin of antibodies. His main question, -what is an antibody, -and some of the answers he offered, defined the immunological debate for half a century, and some of his concepts are still being used by contemporary immunologists (Silverstein specifically mentions the terms of *monovalent* and *multivalent* antiserum, Silverstein, 2002, 81). It was also in this lecture that he introduced his famous receptor theory, which he was to give its most powerful formulation three years later, in his *Croonian Lectures* (Cambrioso, Jacobi et al. 1993).

As a result of the successes of bacteriology and immunology, immunological research boomed, and by the turn of the century new phenomena were discovered almost daily. A consequence of this development was that the distance between theory and practice grew: immunological phenomena were discovered that could not be easily accounted for within existing theoretical frameworks. Whereas the early days of immunology had been concerned with infectious disease, asserting exo-toxins liberated from bacteria to be the only cause of pathology, numerous discoveries were now made of immunological phenomena that did not

[37] Exspressed by Ehrlich as follows: "The reaction of toxin and antitoxin takes place in accordance with the proportions of simple equivalence...*A molecule of toxin combines with a definite and unalterable quantity of antibody*" Ehrlich quoted in (Mazumdar 1995:116).

fit neatly into this picture[38]. The functions of antibodies turned out to be far more many-sided than first asserted, significantly through the discovery of the diverse functions (in the blood) of *precipitation*, *agglutination* and *hemolysis*. These phenomena would concern themselves also with other agents than bacteria, such as the haemolysis of erythrocytes, spermatozoa and proteins (Silverstein 1989). Furthermore, the growing number of antibodies posed problems by itself, as it became increasingly hard to fit them all into one and the same theoretical framework. Hence it came about that when Ehrlich eventually set about to articulate a coherent theory to account for his results, the receptor theory, the field had already outgrown the theoretical framework within which it had arisen. According to Silverstein, Ehrlich, by entering upon the more theoretical aspects of the toxin/antitoxin reaction, went from an experimental approach in which his theories were controlled 'almost entirely by data' to a period were 'theory outpaces data' (Silverstein 2002:55). Eventually, immunology would leave its golden age: highly abstract chemical and physical conceptions would come to dominate the field until biology re-entered it in the middle of the nineteenth century (Silverstein 1989).

At more or less the same time as Ehrlich entered upon these theoretical problems, the dynamics set in motion through the success of anti-sera were working their way into the deeper structures of production and social regulation. In 1894 he had signed a fifteen year contract with Hoechst, who by far came up as the main producer of diphtheria anti-toxin. In 1903 the company announced a record sale of 20 000 litres over the last ten years, earning the company close to 4 million marks. In the publication of these results the company underlined its close connection to the academic scientists Koch, von Behring and Ehrlich. Von Behring, who had helped the company set up its anti-sera production in the first place, left out of a concern that he was being cheated of profits of the sale. Ehrlich, however, continued to have close connections with the company. Significantly, the company came to hold many patents in his name (Liebenau 1990).

In 1899 the Steglitz Institute moved to Frankfurt am Main. Among the reasons for that move was the presence of many prominent pathologists in that city (among the Ehrlich's cousin Carl Weigert) and strong support from local politicians, among them the Mayor of the city. But there was also the presence of the Hoechst Company and Casella & Co. The new institute

[38] Today, it is held that the body may produce antigens against almost *any* substance, be it bacteria, exotoxins, proteins, cells from other animals, plant products etc. (Tauber 1997).

in Frankfurt eventually came to exercise three main functions: testing, service and research. First and foremost, the institute was to serve as the central testing facility for all government-controlled sera sold in Germany. In accordance with earlier practice it would also continue to issue standards for the manufacture of serum. Second, it was to have a servicing function towards the physicians and hospitals, the hygiene movement as well as the military service of Frankfurt. A small laboratory performing tests of incoming samples made up an important part of this work. In addition there was also an educational element in which the Institute would inform about bacteriological, serological and hygienic measures. Lastly, it was to continue research into the deeper functioning of immune reactions and serology. Nowhere along the lines of these functions, it seems, was the close connection to industry questioned: "The relations between the laboratory's functions as a testing facility and as a promoter of antitoxins was close indeed. In a sense, the government laboratory was simply endorsing Hoechst biologicals" (*ibid*.).

Ehrlich himself would eventually come to have serious doubts concerning the developments instigated by himself and his colleagues. Observing the fast-moving expansion of bacteriology and immunology into the pharmaceutical industry, he came to lament a deviation from the programme of the positivist ethos and its devotion to the main goal of medicine, namely that of producing therapies:

"To the initiate, the lack of sufficient positive knowledge is revealed by the inactivity which now characterizes a field once entered upon with so much promise. The innumerable drugs which have overwhelmed medicine in the past few years, of which only a few are of any value and thus denote any real progress, have sufficed speedily to allay the original enthusiasm. A feeling of indifference has thus been engendered, which is constantly being increased by the advertisements which are daily becoming more and more evident. Apart from these evils, however, this line of study is at present suffering especially from two other evils: 1) the habit, when a drug has been partly accepted, of immediately following it with a dozen rivals of similar composition, and 2) the exclusive preference given to drugs acting purely symptomatically, which are not true curative agents" Ehrlich quoted from (Liebenau 1990).

On Liebenau's account these shortcomings were seen by Ehrlich, not as problems rising from social structure or from the role of industry, but rather as an illegitimate intrusion of chemistry into the disciplines of physiology and pathology. The field had to be taken back from the chemists, who did not have the goals of medicine in clear view. This was articulated in a call for a "purely biological" program which was to be put into action on an experimental basis. However, as seen in the previous descriptions, Ehrlich's conception of the "biological" was already heavily indebted to the (stereo-) chemical point of view. We have already seen how

Bernard had argued in a similar vein: although accepting the experimental methods of chemists and physicists, the life sciences were to establish their own way of experimental and theoretical analysis in accordance with the conception of the internal milieu. Compared to Bernard's internal milieu, however, Ehrlich's program stood out as strongly chemically inclined.

Subsequently, he would not stray from the path of chemical specificity, but rather continue to develop it: *theoretically* in terms of the receptor theory, *therapeutically* in a program of chemotherapy in which the actions of antitoxins were to be reconstructed chemically (Liebenau 1990). Before concluding this chapter I will briefly touch upon these two subjects.

I have already referred to several problems encountered by the attempt to establish a scientific account of immune reactions. The lock-and-key metaphor provided the clue to physiological speculations concerning the origin and nature of antibodies. In Silverstein's words: when a toxin binds to a specific site in the organism it "…can only be due to the presence in the receptive tissues of specific receptors that pre-exist there to mediate not only the localization but also the physiological activity of the toxin", (Silverstein 2002:80). Concerning the origins of this complementarity further speculation would be futile, the answer presumably deeply hidden within natural history.

Similar to Bernard's account of pathology as a quantitative deviation from normal physiological functioning, Ehrlich came up with the idea that antibodies are products of the cells *normal functions*. In their original state, they are receptors produced by living cells in order to bind substances to its surface, hence part of its normal metabolism. Primarily, this meant that the receptors, or side-chains as he would also call them, were responsible for binding nutrients to the cell surface. This would also provide a possible explanation of drug action, -drugs act on specific cells because of their complementarities with the specific receptors of that specific cell. Antibodies then, Ehrlich argued, are nothing but receptors responsible for binding antigen to the cells surface. When the cell is attacked by toxin/antigen, its receptors are blocked, and the cell cannot any longer receive the nutrition necessary for its continued existence. The response of the cell will be to compensate, or even over-compensate, for this loss of physiological function by the production of new receptors. These are next shed into the blood (serum) were they connect to the haptophore group of the toxin/antigen so as to

render it incapable of further attachment. Hence the existence of circulating immune serum (*ibid*.).

A similar model was also used in the construction and effectuation of Ehrlich's dearest idea, -that of chemotherapy. In short, the idea was to synthesise chemical substances that would interact with infectious agents in a way similar to that of the biologically produced anti-toxins. However, the task would be much harder, as the active substances had to be constructed rather than simply discovered. Not only did this concern the therapeutic agent itself, -vehicles for transporting it to its specific site of action within the organism would also have to be found (Silverstein 1989). Ehrlich's plans for a renewed therapeutic program were supported by local forces, and in 1906 a new medical research facility appeared in Frankfurt, -The Georg Speyer Haus. Research in the new facility was split into two different departments: one working on biological, the other on synthetic agents. The work culminated with the making of Salvarsan, a chemical curative for syphilis, which was marketed in 1909 (Liebenau 1990). The drug became a huge commercial success and it remained on the market until after World War I. Although that particular drug became a huge success, Ehrlich's vision of a "magic bullet", -a chemical drug with no side-effects, never materialised (Silverstein 1989). One specific outcome of the event was that the relations between state, science and industry were pulled tighter: "Salvarsan was developed at the Speyer Haus, controlled by and with the backing of the government institute, and patented, produced, and marketed worldwide by Hoechst" (Liebenau 1990).

Summing up…

Ehrlich's experimental and methodological approach to immunology supplied the discipline with a unified method. This came about both as a result of his chemical approach, which established a quantifiable object for use in the laboratory as well as in the clinic. The impact of such a unified platform was enormous for both immunology and the medical action system as such. According to Thorvald Madsen, one of the leading immunologists of the day, "Ehrlich's method of measurement [of toxin and antitoxin] is the common property of all civilized nations", and "Ehrlich's immunity unit plays the same role for antitoxin measurement as does the Standard Meter for the measurement of length" Madsen quoted from (Silverstein 2002:51). Indeed, Ehrlich's methods were spread worldwide: in the aftermath of World-War I, they were distributed globally through the Biological Standardisation

Committee of the League of Nations. And the clinical results, as could be stated with unusual certainty, were highly effective:

> "Ultimately, the use of formolized diphtheria toxin as toxoid, adsorbed onto aluminium hydroxide or hydrated aluminium phosphate and given in two doses, has resulted in the virtual disappearance of diphtheria in the industrialized nations. The enforcement of childhood immunization, in the form of DPT (diphtheria, pertussis and tetanus) inoculations, has substantially banished each of these diseases as significant public health concerns" (*ibid*., 52).

However, as we have seen, the astonishing results did not come about as the exclusive result of theoretical mediation, on the contrary, -Ehrlich's attempts at theoretical reconstruction of immune reactions went beyond experimentation and into the domains of what Canghuilhem would term "scientific ideology" (Canguilhem 1991). Says Arthur Silverstein: "Fortunately, the practical value of Ehrlich's protocol for the standardization of diphtheria toxins and antitoxins did not depend on the validity of his theoretical concepts"(Silverstein 2002:60). Concerning the conception of the counterfactual organiser, then, it is clear that it did not reside in Ehrlich's account of immune reactions in terms of stereochemistry, but rather in the more general *episteme* of specificity, introduced to the experimental setting by Robert Koch and carried out within a wide range of disciplines up until the 1950s (Mazumdar 1995; Kay 2000). Within immunology competing notions of immune reactions turned up, as the physicochemical approaches of Bordet and Madsen, or the biological approach "proper", developed after Metchnikoff's idea of phagocytosis (Silverstein 1989; Tauber 1997). The central point is that whereas the general of specificity certainly had much going for it, and so came to function as an organiser across fields of action and knowing, it was never pinned down to a distinct theory about immunity. The success of immunology took place before it was articulated within something resembling a coherent theory. Many of the improvements made by Ehrlich concerned themselves with techniques of standardisation and purification, many of which were outcomes of experimental genius, but they were not derived from Ehrlich's theoretical work.

Concerning the institutional aspects of the matter, Ehrlich found himself in an extremely privileged positioned at the centre of state regulation, product development and research. Although lamenting the course taken by developments, which he saw as moving away from the vision of positive knowledge standing in the service of therapeutic ideal, he still was in the position of exercising considerable control in all the important domains concerned with the

new therapeutics. Concerning the patenting of new products as well as their development *and* quality control, Liebenau states that:

"The patents...had to be owned and defended by a powerful organization. Ehrlich also needed that power, to be able to control the vast productivity of his research team. Furthermore, the products of the research itself could not be made available until after the work was finished to the standards of the laboratory" (Liebenau 1990).

It may therefore be inferred that both the positivist ethos of research and the organiser of specificity already had had their hay-days, and that they increasingly entered into organisational and theoretical complexities in which they would no longer run smoothly along with developments. Still, the discoveries within immunology and bacteriology would continue to work their ways into society with remarkable degrees of success well into the interwar period. What took place may therefore be regarded as a double movement: a gradual expansion of anti-sera production and control conducted by Ehrlich in close connection with industry and regulatory apparatus, *and* rising problems of supplying a theoretical and experimental account of immune reactions (*ibid*.). Within this double movement we may identify dilemmas that will, in the later case of genetics, come to spell out as problems of regulatory legitimacy: the decoupling of experimental and theoretical command from social forces recast and given momentum through experimental intervention itself. It will also be argued that a particularly strong promoter of these developments is the close connection to industry, which will later (i.e. in second modernity) also come to introduce strong movements of (relatively) free-floating capital, rendering the academic-industrial relations ever more unstable and unpredictable. Hence, borrowing from both Beck and Heidegger, we may state that projections of the academic-industrial complex were made by Ehrlich and his colleagues that would later re-enter the experimental systems in the transformed version of venture capital.

5. Trajectories of the gene and its organisation

Several powerful metaphors have been invoked in order to describe the gene and its organisation. Both in the fields of basic genetic research and in the literature describing this research, the functioning of the metaphors of *information* (Kay 2000) and *mapping* (Bostanci 2004) have been central. As have already been argued I take it that these metaphors are important primarily because of their significance for the organisation of action.

The notion of action has also been a powerful metaphor during the construction of the gene. The concept of action and its intermingling with the gene has been articulated by Evelyn Fox Keller (Fox Keller 1995; Fox Keller 2000; Fox Keller 2002). Specifically: the significance of the concept of action hinges on the ways in which we ascribe causal *agency* to the gene and, correspondingly, the social and material configurations and re-configurations thereby entailed: What does the gene do? What can we expect from it, and, considering the needs in medicine and health care: how can it be put to use in the best possible manner?
notions of action and language. I adopt a perspective on the history of the gene that is closely related to that of Fox Keller. However: as institutional, political and economic perspectives are downplayed in her expositions, it is necessary to borrow from other theoreticians, significantly Lily Kay, Pnina Abir-Am, Susan Wright and Gaudilliere, Rheinberger et. al. Furthermore, Fox Keller often undertakes rather broad sweeps of the field. These other writers are therefore important also in filling out details concerning technologies, experimental activity and material agency.

Historically speaking then, I base my exposition upon three different stages of development as given by Fox Keller and the different notions of gene action entailed in each:

1) *Classical genetics*, lasting (roughly) from 1930 to 1960. In this period, causal agency is ascribed to the gene "itself". Hence, this is the period in which the notion of "gene action" arises and is given its most literal interpretation.
2) *Early molecular biology*, 1960 to 1980. In this period, the notion of agency is transposed from the gene "itself" to that of the *genetic program*.
3) *Post-recombinant DNA (developmental) molecular biology*, lasting from 1980 to 2000, in which the *genome* is conceived as the fundamental unit of genetic action and information (Fox Keller 2002:113).

Needless to say, categorisations like these should not be taken too literally, but should be read as historically situated analytical categories. We are talking about gradual developments in which one period is not simply "replaced" by another, but rather transformed (*Aufgehoben*) into the next. Hence, the notion of gene action does not disappear even if replaced by the genetic program:

> "…the explanatory force of the terms gene action, feedback, genetic programs, and positional information relies upon and makes use not only of their function in disparate contexts from which they were borrowed but also of the functions of earlier terms and earlier forms of explanation in genetics that may not longer be explicitly invoked" (*ibid.*, 114).

The usefulness of metaphor for experimental activity has been extensively studied in the literature about science and technology[39]. The notions of gene action, the genetic program and information are described by Fox Keller as fundamentally ambiguous terms: they are metaphors of something else, something that we do not quite know what *is*, and so they may be ascribed even contradictory properties. Perhaps a bit surprising for those used to think of science in terms of accurateness and exactness: Fox Keller draws the conclusion that without the plasticity of central biological concepts, research would never get started in the first place. This is possible because we are talking about two different levels: concepts like gene action and the genetic program are reflective constructs used to give unity to experimental phenomena, but they are not themselves identical with these phenomena.

Gene action

The concept of the gene in the 1930s was exactly such a strange creature. It was given the responsibility for widely divergent functions: on the one hand it was to account for patterns of inheritance as described in the formalistic Mendelian crosses. On the other hand, it was also to account for the concrete development of the organism as such. Hence, the gene was functional both as a determinant of inter-generational *transmission* and of the *development* in the single organism (the two were united through the conception of causal agency: the ability to act as a prime mover in two directions simultaneously).

As described by Fox Keller, this double function of the gene corresponded outwardly to an attempt at a disciplinary take-over: the notion of development had originally belonged to

[39] The classical example being the studies undertaken by Mary Hesse (Hesse 1980). Fox Keller has also devoted one book explicitly to the subject (Fox Keller 1995).

embryology, whereas the transmission of inheritance belonged to genetics (a distinct discipline since 1909, when the concept of the gene was coined by Wilhelm Johannsen). Now the gene was also called upon to account for embryonic development. If the causal primacy of the gene could be established also in this field, embryologists would have to acknowledge the authority of the geneticists.

However, as the material basis of the gene was still unknown, genetics was treading the same waters as other biological disciplines of the day. Biochemical and biological action and reaction was, as already described in the previous chapter, to a large degree explained in terms of *specificity*, a concept already central to a wide spectrum of disciplines. The notion of specificity had acquired its technical and scientific meaning mainly through its successful use within immunology in the beginning of the century (Mazumdar 1995). But it had also proven a useful organiser within other disciplines such as bacteriology, enzymology and taxonomy. In short: even before the material basis of specificity had been established, it was proving its usefulness in a number of experimental contexts. It was known that enzymes, bacteria, organs, antibodies, species and genes were possessive of high degrees of specificity, and it was furthermore *assumed* that these were determined by *protein structure*. Roughly speaking, basic physiological research from the twenties to the mid 1950s took place within a protein paradigm (Kay 2000).

Up until the early 1930s, however, genetics was not part of experimental physiology, but was carried out more or less in the classical Mendelian sense, notably by T.H. Morgan. Insofar as it was concerned with experiments upon the fruit fly *Drosophilia*, it was of course an experimental science. But compared to the interventions of biochemistry, it remained abstract with its reliance upon models and linkage maps, and for Morgan the gene remained a theoretical entity (positioned somewhere on the chromosome).

If we expand the notion of intervention to the social level, however, it becomes misleading to state that genetics was non-interventionist. From the time of the rediscovery of Mendel's laws in 1900, genetics came to be closely associated with the eugenics movement. I am not going to give a detailed description of that movement here, but restrict myself to noticing the following: In these early days a large number of geneticists were supportive of the movement, and their work willingly found its way into popular works and eugenic programs. As the movement expanded into social policy, many withdrew their support, not the least because of

the simplistic, quasi-scientific inferences involved in the program. But active public resistance towards the possible misuses of genetics was not notable until the atrocities of the Nazis were revealed (Beckwith 1996). In 1939 central geneticists like Muller and Haldane, who earlier had been supportive of the movement, would sign a manifesto that actively condemned the use of genetics for eugenic purposes. But, as noted by John Beckwith, "for the most part, the influence of geneticists on the misapplication of their field was too little and too late and thus had a minimal effect" (*ibid.*)[40].

Although T.H. Morgan did not himself take an active part in the eugenics movement, early in the century his works came to be associated with the American Breeders Association, an organisation that championed eugenics (Kimmelman 1983). And later, as an advisor to the Rockefeller Foundation, he argued in favour of the active application of physical and chemical interventions as means for getting to biological structure (Fuerst 1982). Although itself not a eugenic program, it remains an undisputed fact that the program of the Rockefeller Foundation would promote the use of physiological intervention to improve upon the human stock (Abir-Am 1982). There is a lesson, pointed to by John Beckwith, to be learned from the historical cases of eugenics and the program of the Rockefeller Foundation. It has to do with scientific reductionism and it has to do with the interventions, scientific and social, thereby rendered possible. The levelling of physiological function onto one explanatory level, such as that of the gene, is not only pursued for the sake of knowledge itself, but has some potential use in terms of standardised and rationalised action on the social level. On a diagnostic level, this poses a danger insofar as it also facilitates the classification of human beings across a wide range of social, physiological and cultural differences. Taken a few steps further, genetics may also serve to diagnose "conditions" normally ascribed to the social dimension, such as unemployment, musicality, race and so on. Today we see this honourable tradition continued by sociobiology (Rose 1997).

Without wishing to go too deep into the "reductionism/anti-reductionism debate": there is a social fact of the matter about efforts to reduce a great number of organismic, psychological and social factors to one level of explanation only: it also facilitates the standardisation of actions towards social or cultural groups on a broad scale. This may turn out as useful to society, but it may also turn out very ugly indeed. In Norway, following World War II, Nazi

[40] In 1969, Jonathan Beckwith, then at the Harvard Medical School, led the first team of scientists to isolate a single gene.

sympathisers were diagnosed as mental deviators. 1100 women known to have had relationships with German soldiers were internalised on the "Hovedøya", an island outside of Oslo (Hviid Nielsen, Monsen et al. 2000). Obviously there were strong social and historical reasons behind the resentments against these women that were, regarding the post-war situation, quite understandable. But this does not excuse the (mis-)use of scientific arguments.

When applied to genetics, specificity would read as follows: one gene – one trait. Morgan and his research group had long rejected the ascription of such specific action to the gene. The reasons behind Morgan's initial rejection of this connection were disciplinary rather than scientific. Strange as it may seem today, geneticists and embryologists had for many years shared work between them: genetics study transmission of heredity, embryology the development of the concrete organism. But in the long run, this division of labour made little sense: "…what would be the point of tracking the transmission of hereditary factors unless these factors can be assumed to be implicated in the formation of the traits or characters that distinguish an organism, that is, in its development?" (Fox Keller 2002:125). The search for an answer seemed to be driving in the direction of the molecular level, hence also towards radically different research methods.

However, the embryologists had a strong research program of their own, and if their preferences were different from those of classical genetics, they were even more opposed to the methodologies and the views upon basic physiological functions found within the new discipline of molecular biology. As pointed out by Scott Gilbert: If molecular biology was the science of the genotype, embryology was the science of the phenotype. Whereas the new biology took its inspiration as well as its methods and technologies from the physical sciences, emphasising genetically regulated cell differentiation as the motor of development, embryologists would study development on an altogether different level, namely that of morphogenesis (Gilbert 1996). Here then, we have two radically opposed views of what physiology is supposed to be. It is also clear that, at the time, it was in no way determined in which direction developments would move. Within the framework of the main paradigm of the period, that of protein structure, embryology indeed possessed authority in matters of inheritance and development: "…experimental embryology…was equivalent to the 'molecular biology' of the 1930s in terms of its revolutionary potential for solving the then major problem of biology – the problem of biological order" (Abir-Am 1982).

In 1878 Claude Bernard had stated that the goal of studying living phenomena was to uncover the "hidden design", the organisational principle underlying development and physiological function (Fox Keller 2002). (Classical) embryology, proceeding from ordered form as a functioning whole, took this principle to reside in the cytoplasm and to be studied on the level of tissues, not by recourse to the cell nucleus. In the study of differentiation and development, this choice of level makes quite a difference, methodologically, technically and institutionally. Geneticists, of course, would take the hidden design of the organism to reside first in the gene, then in the genetic program, and then in the genome. In 1970, referring to Bernard's "hidden design", Francois Jacob wrote that "Not a word of these lines needs to be changed today", quoted from (*ibid*., 141).

Influenced by the physico-chemical approaches within immunology, genetics came to be seen as an important tool in the research program of the Rockefeller Foundation. Also Morgan, by then acting as advisor to the foundation, came to endorse this broadening of the scope of genetics. Notably: if genetics could be linked to experimental *intervention* (Kay 1996), it could also become a powerful tool for social engineering.

> "It is within the new agenda of physiological (or physico-chemical) genetics that specificity gained direct relevance to gene action. And as in the other life sciences, the notion of specificity was transported into genetics from immunology through the nascent field of immunogenetics. Serological studies from animal systematics had demonstrated a direct relation between the formation of antibodies and heritable genetic markers, relations with immense promise for eugenic intervention. With the intensified programmatic development of physiological and biochemical genetics in the 1930s, the relations between genes and their products came to be conceptualised in terms of biological and chemical specificities" (Kay 2000:45).

The main problem consisted in establishing how this worked. Taking inspiration from the physical and chemical sciences, it seemed that there would have to be some basic unit, like the atom, possessive of the necessary agency. It also seemed that this seat of agency, the gene, would have to work in two directions simultaneously: as reproducing itself into the next generation *and* to determine the properties of the organism through the mechanism of cell differentiation within the single generation. How could the structure of the gene translate into function? (Fox Keller 2002). One direction of research that later proved immensely influential went by situating genetics within biochemical reactions in the study of unicellular organisms.

Embedding gene action: Model organisms

In the early forties some progress was made towards experimental demonstrations of the specificity of gene action. One such event was the demonstration of the so-called one gene –

one enzyme reaction established in the fungus *Neurospora* by George Beadle and Edward Tatum. The studies of *Neurospora* did not so much grow out of genetic research as out of biochemical and bacteriological studies of metabolism in micro-organisms. Up until then genetic studies had been carried out mainly on the fruit fly *Drosophilia*, a diploid organism. How could traditional genetics, presupposing sexual reproduction, be applied to haploid organisms[41] like fungus, in which the existence of chromosomes remained highly uncertain?

One central part of the answer went as follows: it was assumed that the study of *mutations* in micro-organisms would prove *analogous* to sexual reproduction in diploid organisms (Creager 2004). How was this analogy established?

In the 1930s extensive studies were made of reproduction and nutrition in bacteria. It had earlier been observed that bacterial cultures underwent morphological changes. Could these be attributed to mechanisms of sexual reproduction? Furthermore, biochemical studies of metabolic pathways in micro-organisms were central to nutritional research in the interwar period (*ibid*.). One important way of carrying out these studies went by the induction or inhibition of growth factors for bacterial cultures that had been grown on chemically definable media. By such manipulations, biochemists were able to study specific changes in metabolic pathways.

Beadle and Tatum built upon these techniques and developed them further by mutagenising *Neurospora* with X-rays. In that way they were able to produce a far greater amount of variables in the original culture in the shape of mutants with changed nutritional requirements. For instance, one mutant would be unable of synthesising the vitamin pyroxene. It was then assumed that these mutations were attributable to changes in specific parts of metabolic pathways that were controlled by specific enzymes. By cross-breading the mutated spores with wild-type spores it became possible to observe mechanisms of recombination which next could be subjected to traditional genetic linkage maps. The first established mutation, that of pyroxene, recombined in a manner that could also be predicted on Mendelian principles, and

[41] The notions of haploid and diploid refer to sets of chromosomes. Whereas diploid organisms have two sets of chromosomes, haploid organisms have only one. For sexual reproduction to take place, two sets are necessary. Through the process of *meiosis* the sex cells, with one chromosome set only, are produced. Traditional Morganian/Mendelian studies of gene recombination presupposed these mechanisms for establishing genetic linkages.

so it was assumed that the mutations, hence also biochemical reactions, were genetically controlled.

Following up on the *Neurospora* experiments, Tatum, now in collaboration with Joshua Lederberg, went on to apply the same techniques to the bacteria *E. coli*. At the Cold Spring Harbour Meeting in 1946 they were able to present ample evidence that different (growth inhibited) mutant strains of *E. coli* would also undergo genetic recombination when mixed on a minimal media (that is, nutritionally un-supplemented) (Fruton 1999).

At the same meeting, Alfred Hershey reported experiments demonstrating that also bacteriophages (bacterial viruses) would undergo something very similar to genetic recombination. He carefully pointed out that viral genes were defined by way of mutation and not by segregation/recombination, but that mutation may prove *analogous* to allele segregation in diploid organisms.

Hershey also went on to define the locus of mutation, the "genetic site", as possessing specificity in the sense that it would mutate independently from other loci. A gene, then, would be "the hypothetical structural site of a mutation or set of alternative (allelic) mutations that occur independently of other known mutations" (Creager 2004).

Finally, also this at the same Cold Spring Harbour Meeting, Max Delbrück and William Bailey demonstrated that infection by mixed bacteriophages could result in new viral genotypes. Hence, says Creager, "…many results of 1946 pointed to genetic exchange between viral variants and between *E. coli* strains, opening up the prospect of genetic mapping" (*ibid*.). The mechanisms of bacterial and bacteriophage reproduction remained mysterious until, among others, the mechanisms of transduction, plasmid action and lysogeny were discovered. It then became clear that the recombination of these organisms depended upon both nuclear and cytoplasmic factors. From then on "Bacteria and bacterial viruses quickly supplanted fruit flies as the test-bed for many of the subsequent developments of molecular genetics and the biotechnology that followed" (*ibid*.).

The *Neurospora* studies and the works on *E. coli* and bacteriophage went some way in establishing micro-organisms as model organisms for experiments on the level of the molecule. It was established that Mendelian genetics could also be part of direct interventions

that went far beyond the classical studies on fruit flies. But whereas this went some way in explaining hereditary *transmission*, genetics was still a far cry away from the sought-after explanation of the *development* of concrete organisms. And so we are back to the initial aporia of this chapter: that of uniting the transmission of heredity with the development of the organism within one explanatory framework. The question had, however, been somewhat refined: How was it possible that the genome, presumably always the same in every cell, could produce so different (specific) effects in the single cells, tissues and organs?

In a paper from 1948, "Differentiation as the Controlled Production of Unique Enzymatic Patterns", Sol Spiegelmann posed the problem explicitly in terms of cellular differentiation. Cellular differentiation was, as the title stated, given a biochemical explanation in terms of "unique enzyme patterns" (cf. specificity). Genes control enzymes, enzymes control development. Spiegelmann's study built on premises established in two earlier studies. The first was that of Beadle and Tatum already described, in which the one gene – one enzyme hypothesis was, if not actually proven, then indicated. The second was a study by Greenstein and colleagues, in which it had been established that the cells of different tissues display differing enzymatic pathways. Together, these premises strongly indicated that differentiation was controlled by different enzymes (Gilbert 1996).

Enzymatic adaptation to different growth substances had been studied by enzymologists and bacteriologists since the early 1930s (Kay 2000). Now Spiegelmann and others brought these studies to bear on the problem complex of genes, enzymes and cellular differentiation. By observing the effects of changing the growth conditions of *yeast*, Spiegelmann hoped to cast light upon the much more complex process of embryological development: "One could certainly study the biochemistry of cells much better than in the constantly changing embryo!" (Gilbert 1996). One main reason for using yeast was that the cultures could be halted at different stages of the growth process in a nitrogen deficient medium, thereby rendering it more accessible to study.

By changing the growth conditions the yeast would produce different enzymes, namely those needed to metabolize the substrate on which it was growing. It was then said that the enzyme had been *induced* by that particular substrate. In order to continue the production of that specific enzyme, the continuous presence of the inducer substrate was necessary. One central example was the production of galactosidase by yeast grown on galactose. The yeast studies

were taken by Spiegelmann as indicators of how identical genomes would synthesise different proteins: the difference was caused by the inducer. Furthermore, they said something important about the kinetics of enzyme production. It seemed that synthesis proceeded according to curves descriptive of autocatalytic reactions: the more enzymes already present, the faster enzyme synthesis would proceed. He also drew the conclusion that different enzymatic processes were competing for a limited amount of resources: amino acids and energy. With the notion of autocatalysm in mind, this would mean that the stronger one specific strain of enzyme synthesis got, the less (proteins) there would be for competing systems (*ibid*.).

A comprehensive theory of gene action would have to explain how this competition among cytoplasmic agents (ribosomes were not yet discovered) was controlled from the cell nucleus, i.e. from the genes. By the use of phosphate as a tracer, Spiegelmann demonstrated that protein production took place simultaneously with phosphate movement out of the nucleus. He thus drew the conclusion that there had to be an intermediate transmitter between the nucleus and the cytoplasm, and he termed this the plasmagene (messenger RNA had not been discovered either) (*ibid*.).

Embryology, then, could be founded upon the theory of the plasmagene. Similar conclusions had also been made by others in the field, significantly by C.H. Waddington. Still, the theory remained incomplete. The nature of the main actor, the gene, was still unknown, and there was a general lack of experimental data to back it up. However, there were other and related experiments going on that would further promote the molecularisation of embryology. These were the studies carried out at the Pasteur Institute; also these starting out with the physiology of enzymatic adaptation in bacteria, finally resulting in the discovery of messenger RNA and the notion of the genetic program.

To sum up: until the discovery of DNA as the material basis of heredity, basic physiological research was carried out under a protein paradigm. During this period, biologists came to adopt many of the experimental methods developed within the physical and chemical sciences. For these purposes, model organism like E.coli, bacterial phages and viruses played essential roles. Hence, in terms of experimental action, the study of heredity and development took decisive steps from abstract representations of genes towards interventionist practices (Hacking 1983) through which the chemical basis of heredity would also be illuminated. This

was also the period in which the *promise* of medical utility started to seem a possibility on the horizon. Although classical genetics had possessed a potential opening towards social intervention (i.e. eugenics), it was by embedding gene action that physiological intervention first appeared as a realistic possibility. Important model organisms, like E.coli, bacteriophages and viruses, were introduced to the practice of genetics, and important mechanisms, like transduction, plasmid action and lysogeny were described. All of these would later come to play important roles in genetic technologies.

On social and institutional levels, we may point towards several factors that went hand in hand with the reconfiguration of genetics in a more materialist and interventionist direction:

First, developments within *immunochemistry and bacteriology* had already proved immensely successful, not only on the experimental, but also on the clinical level (previous chapter). Within the protein paradigm it was not far-fetched to ascribe agency to genes much in the same way as agency had been ascribed to the anti-body: as operating stereochemically and as possessive of high degrees of specificity.

Second: *Theoretical physics* was undergoing important changes (Fjelland 1991) from classical to quantum theories of the organisation of matter. These were also carrying non-reductionist implications that, as pointed out by Abir-Am, opened up "conceptual and epistemological spaces for a 'new biology': ideas of wholes, atomic organization and systems" (Abir-Am 1982). One important link went directly from Niels Bohr and the Copenhagen School to the so-called "phage group" at Caltech, headed by Bohr's former student Max Delbrück. In the 1960s, when the founding myths of molecular biology were first created by central actors in the field, this connection did not go un-heeded. James Watson would then derive his own project more or less directly from that of Delbrück, which again led back to Bohr (Abir-Am 1999). This move served both to underpin the historical importance of Watson himself, and to give to molecular biology a sense of robustness by aligning it with physics. But: in the 1930s and 40s these connections were not clear at all. So even though the influence from physics contributed strongly towards the search for the "basic building blocks of life", the further course of events was open, and the drive towards reductionist research agendas was not yet "written in the genes".

Third: actors with interests in the modernisation and rationalisation of society took an active interest in "biological progress". As exemplified by the politics of the Rockefeller Foundation, there was indeed a strong institutional and ideological drive towards deploying the new biology for purposes of modernisation: The term "molecular biology" was coined by Warren Weaver, the foundations Director of the Natural Science Division, in 1938. Prior to research policies following World War 2, philanthropic organisations and private patronage did play a major role in directing and funding research agendas:

"...the research policy instituted by large philanthropic foundations, and especially that of the Rockefeller Foundation in the 1930s, shared a common vision with their later counterparts. In the 1930s, the Rockefeller Foundation's research policy was not only an attempt to provide a firm grip on the course of scientific progress simply for the sake of science, but was also a crucial element in a strategy aimed at maximizing total 'social returns' from science" (Abir-Am 1982).

The program of the Rockefeller Foundation spanned over a wide range of disciplines, and the social (behaviourist) and biological sciences came to be seen as key tools for modernisation and rationalisation. Before it became the molecular biology program, it was called "psychobiology", and it formed part of the larger program of the "Science of Man", having as its main goal "to coordinate the biological sciences, social sciences, and medical sciences toward a comprehensive rationalization of human behaviour in quest of social control" (Kay 1996). One main goal, as well as an operational strategy, was that of transferring technologies from the physical and chemical sciences to the biological sciences. By promoting the application of technologies from physics and chemistry, such as X-rays, electron microscopes, biochemical assays, ultracentrifugation and so on, the study of the organic was supposed to move biology out of its unproductive backwaters. This approach, however, did, more often than not, *fail* to promote the actual goal of "biological progress". According to Abir-Am, the early attempts from the Rockefeller Foundation were strong in physical and economical power, but most of the projects thereby carried out were short on biological knowledge. Weaver and his associates "lacked the basic understanding that people work on problems; they do not merely use techniques" (Abir-Am 1982). However, although lacking in short-term successes, the program did indeed influence further developments:

"If the Rockefeller Foundation was impressed by its own rhetoric and managed to advance clever entrepreneurs, its historical relevance for future molecular biology was nevertheless real. While none of its long-term grantees pioneered a redefinition of biology along molecular lines, Foundation Grants stabilised not only their personal careers but also established their institutions as training centres for users of physical technologies on biological materials. The presence of these "users", in growing numbers colonised biology in the name of a mastery of 'progress defining' technologies. Their sheer

numbers eventually established a new social reality, which claimed the name 'biology', - albeit preceeded by the metaphorical adjective 'molecular' - for individuals who had little knowledge of biology, but who had mastered powerful physical technologies in search of results to sustain careers" (*ibid*.).

Regardless of who caught up with whom: power (institutional/economic) and the different kinds of knowledge involved in the negotiations of the 1930s, *did* indeed reunite in the post-war period so as to give meaning to the efforts of the Rockefeller Foundation. It was this stabilisation of the complex relations between physical technology and biological knowledge that would turn up as the full-fledged discipline "molecular biology" in the early 1960s.

The conception of gene action most certainly found fertile ground within the social, historical and scientific environments of the 1930s, 40s and 50s. Not only did it serve as a necessary stepping stone for geneticists trying to come to grips with heredity and development, it also went along well with modernist agendas *and* the wider developments within the natural sciences; changes in theoretical physics as well as the recent successes of biochemistry. No wonder, then, that the conception of gene action did not possess a precise, scientific definition, and no wonder that this fact did not seem to bother many at the time: there were lots of functions for the gene to play. This did not necessarily mean that the geneticists and biologists of the day were naive; it just means that there were many reasons, scientific as well as extra-scientific, for the concept to be a useful one (Fox Keller 2002). As we have seen, early, "semi- material" definitions of the gene were given through studies of phage and virus. Although no chemical definition was achieved, the gene, and thereby also the conception of gene action, was defined loosely as the loci of mutations (Hershey) or in terms of recombination (Delbrück et al.). As long as the chemical basis of these experiments remained unknown, the conception of gene action also retained its plasticity. In the long run, however, this was not a tenable situation:

"Insofar as the science of genetics was committed to a causal narrative of development, there needed to be a place, a thing, a word to which causal force could be attached, and in the absence of any foreseeable route to a clarification of what that thing might be, it was functionally important to have a word that could contain or black-box its uncertainty and to keep its internal incoherence, as it were, under wraps. Not only did it permit researchers to get on with their work – resolving the problems they *were* able to address, without having to worry about those they could not – but also it provided them with an explanatory framework, albeit a provisional one, with which they could make sense of progress they were making in their day-to-day research, both to themselves and others. That it also served other uses – for example, in the struggle to establish genetics as a discipline and even in

international and gender politics – only means that it was productive in more than one sense" (Fox Keller 2002:132).

In fact, says Fox Keller, the conception of gene action was not only a metaphor, -it was a "metaphor of a metaphor". The speculation about what the gene might actually *be* was *not* clarified until the elucidation of its chemical structure in 1953. So, while awaiting an affirmative answer, the question as to the gene's material basis had to be suspended. But if the gene was to organise any experimental action at all, the least one could expect was some notion of what it is that the gene *does*. In an almost perfect tautology, the answer went that the gene *acts*. Because there was no firm point of reference for answering the question as to what the gene actually does, it was likened to that which we do know, namely *agency*. In that manner, the circle was completed: the question as to what the gene *is* was answered in terms of what it *does*, and the question as to what it does was answered in terms of what it is, namely an agent. In that way, the gene was invested with agency. It was, we may state, created in the image of man, and at the same time it was inscribed with almost divine powers: Those of reproducing itself infinitely and, at the same time, of being the cause of concrete developments in the single, finite, organism (Fox Keller 2002).

Being as it is science that we are talking about here, the inherent tautologies of gene action could not go unheeded for long. Indeed, during the 1940s some sobering-up was achieved: in 1944 Avery, MaLeod and McCarty demonstrated experimentally that *nucleic acids* were the carriers of specificity in pneumococcus bacteria, and in 1946, as already described, Tatum and Beadle went some way in embedding genetics in studies of metabolic pathways in *Neurospora*. As also described by Abir-Am (above), this increasing ability to *intervene* so as to establish genetics as experimental physiology also corresponded to the re-coupling of instrumental, institutional and economic power with basic biological knowledge and experimental competence. However, assuming that this process of learning peaked with Watson and Crick's elucidation of DNA's structure in 1953, the notion of gene action was also thereby *dis-empowered*. When there was no longer any reason for doubting the chemical basis of the gene, it also lost many of the properties earlier ascribed to it:

"…the discovery of the structure of the double helix, together with that of a correspondence between sequences of nucleotides and sequences of amino acids, did (or so it seemed at the time) cleanse the concept of the gene of all residual ambiguity. But for the purposes of explaining development, these findings also cleansed it of its force…Thus, for a satisfying global narrative of development –

especially, for an account of how genes may direct 'some cells in the embryo in one way, some in another' – a new linguistic construct would be needed" (Fox Keller 2002:134).

This new linguistic construct would come in the shape of the genetic program. As will be seen, the gene, or, rather, the genome, thereby *regained* many of the properties ascribed to it in the terms of gene action, this time on a higher level of complexity. This did not make the concept less strange than its precursor. As described by Fox Keller, the inconsistencies of gene action were brought along -and some new ones were added.

Closing the space of development

The importance of deoxyribeonucleic acid (DNA) within living cells is undisputed. It is found in all dividing cells, largely if not entirely in the nucleus, where it is an essential constituent of the chromosomes. Many lines of evidence indicate that it is the carrier of a part of (if not all) the genetic specificity of the chromosome and thus of the gene itself (Watson and Crick 1953).

After the elucidation of DNA structure in 1953 by Watson and Crick, one major experimental problem was how to relate this structure to the protein synthesising machinery of the cell (the problem of hereditary transmission being regarded as solved trough the mechanism of DNA replication). How did the four nucleic acids translate into the twenty or so amino acids that went to synthesise proteins? If the notion of specificity was to apply to these chemical (re-)actions, there seemed to be a missing link: how did the message get from the nucleus to the cytoplasm?

In 1965, Andre Lwoff, Jaques Monod and Francois Jacob would share the Nobel Prize for their work elucidating these connections: For demonstrating some of the central specifities and regularities in the interactions of genes and proteins; for elucidating the regulation of these by the genetic program, and for discovering and demonstrating the role of messenger RNA in this process (Kay 2000:195).

An important precursor of the studies that underpinned these discoveries was the (biochemical) works on microbial physiology carried out by Andrè Lwoff in the 1930s. These were specifically focused on the role of enzymes in regulating metabolic pathways. Two main features of this research went as follows. First: enzymes are not created from something else; they arise from other enzymes. These results were primarily derived from experiments in which specific pathways of carbon digestion in micro-organisms were singled out and their function related to the presence or absence of specific enzymes. Second, they developed

precise techniques for elucidating these mechanisms. Through the cultivation of stocks of cultures whose characteristics were known and through the deployment of minimal media that were biochemically well defined, they were able to trace lesions in metabolic pathways with great precision. These techniques also came to play a central role in the experiments of Beadle and Tatum (Burian 1996).

At the time of Lwoff's studies, the growth of bacteria was depicted as depending on the media on which they had been grown. Changing the media would also change the metabolism of the bacteria. These changes, it was assumed, furthermore depended on two types of enzymes, termed respectively *adaptive* and *constitutive* enzymes. Adaptive enzymes would be synthesised only in the presence of specific substrates in the medium, the substance being for instance a sugar, the enzyme then being formed in order to metabolise carbohydrates. Constitutive enzymes, on the other hand, would continue to be formed regardless of the presence of any specific substrate in the medium. This division corresponded to a central problem in microbial physiology that has already been mentioned more than once. This concerned the mechanisms controlling enzyme biosynthesis: were they primarily genetic (constitutive) or were they chemical (adaptive)? The question carried both theoretical and ideological implications: the adaptive point of view stressed the impact of the environment and the organism's capability for learning from its surroundings and was typically associated with Lamarckism, dominant in France at the time. The other point of view (Darwinian) would represent development in terms of randomness and spontaneous mutations rather than smooth co-existence with the environment[42]. In this way the problem also came to bear on the old issue of the basis of inheritance: was it nuclear or did it reside in the cytoplasm? (Kay 2000)

The answers given by the Pasteur group would further dispel the mechanisms of reproduction and metabolism from the cytoplasm and place it within the closed-off space of the nucleus. This was done through a conceptual change in which the old vocabulary of biochemistry (proteins) was recast within a discourse of *information*, systems theory and cybernetic metaphors. Centrally: The above mentioned distinction between adaptive and constitutive was no longer to be regarded as fundamental properties of enzymes, but rather as properties of biological systems. Adaptivity was furthermore dispelled from the conceptual apparatus and retranslated as *induction.* Also induction would be taken to mean a heightened degree of

[42] Through the Lysenko affair, these issues gained a direct political relevance: The credibility of biology had been questioned on the international political arena.

synthetic activity in the presence of some substance external to the bacteria, but now with an extra clause added: it was controlled, not by the external substance, but by an endogenous *inducer* (*ibid*.).

One important reason for this change of vocabulary was experimental: many cases of so-called "nonadaptive behaviour" had been observed in micro-organisms. Max Delbrück and Salvador Luria had demonstrated (1943) that many changes in bacterial physiology do not take place in the form of smooth adaptations to their environments, but rather in terms of seemingly random and spontaneous mutations (Fruton 1999).

Jaques Monod was definitely on the side of the neo-Darwinians: his projects in the late forties were designed to dispel the notions of teleology and last causes from French biology. These attempts would also come to go hand in hand with his program for modernising the same science and to establish molecular biology at its centre. Together with his assistant Melvin Cohn he had studied enzyme synthesis in *E. coli* and made observations that seemed to go against the prevailing Lamarckianism. First, they discovered that lactose could inhibit the synthesis of beta-galactosidase (so-called end-product inhibition). They reasoned that the inhibitory force operated independently from the lactose-galactose interaction itself and that it had to rely on an inductive mechanism of the bacteria. Inhibition of galactosidase was not an outcome of this chemical interaction but of something else. They furthermore observed that *E. coli* bacteria constitutive for the production of galactosidase would continue to synthesise the enzyme even in the absence of galactose in the growth medium. It seemed pointless that the bacteria should go on producing an enzyme that could not be used to metabolise the substrate. Also this pointed in the direction of genetic control and away from contextual and environmental explanations (Kay 2000).

In the 1950s Francois Jacob and Elie Wollman had been studying the genetic organisation of bacterial sexuality. Central to these studies had been recombinations between the genetic material of *E. coli* and bacteriophages (bacterial viruses) that would eventually cause lysis when inserted into the bacterial host (i.e. the bacteria would dissolve). "Male" bacteria carrying phages in a non-active state (so-called pro-phages) were shown to induce lysis in recipient, "female" bacteria that from the outset of were non-lytic[43]. By the use of a blender

[43] For a feminist reading of these metaphors, see Fox Keller (1995).

they were able to interrupt the mating of the two bacteria, and so it became possible to study the exchange of genetic material in its different stages. Surprisingly, it was revealed that the recipient bacteria, the "female", for a short period of time after the mating process would exist in a diploid state, i. e. it was possessive of two pairs of chromosomes. This "zygotic technology" was then taken as confirmation that the mating process of bacteria was (more or less) the same as in higher organisms (Kay 2000).

In earlier studies, Jacob had also made observations on prophage activity that would become central. By exposing lysogenic bacteria to ultraviolet radiation he discovered that the radiation would act as an inducer so as to make the prophage burst (causing lysis in the bacteria). This phenomenon would later become known as the removal of some inhibitory mechanism working on the phage so as to stop it from bursting (derepression). A similar phenomenon was discovered to reside naturally in bacteria immune to phage lysis. It was then assumed that immunity was another such repressive mechanism operating on the level of the phage genome.

In a classical series of experiments that would be known as the "PaJaMa" experiments, Monod, Jacobs and Arthur B. Pardee used the zygotic technologies developed by Jacob to study the genetic control of the lactose synthesising system of *E. coli*. Following and further developing the methods of Beadle and Tatum, Monod had isolated three so-called lac-negative mutants, bacterial cultures that were unable to grow on lactose even though they were constitutive for the enzyme beta-galactosidase[44]. The phenomenon was explained by reference to the absence of another enzyme, permease, assumed to concentrate the basic units of lactose in the cell. The lac negative mutants were assumed to lack this enzyme, thereby also rendering them unable of metabolising beta-galactosidase. It was furthermore assumed that synthesis of the two enzymes was genetically linked. These relations were now studied by inserting the mutations in male and female bacteria, thereby adding a new dimension to the experimental techniques of enzyme analysis:

"The experimental system was altered. The conjunctions of the E. coli and phage systems now produced a composite experimental system and hybrid technologies, thus reconfiguring the experimental space, once again, to include new graphemes: representations of enzymatic functions in terms of genomic maps" (Kay 2000:212).

[44] Monod had received the specific strains of *E. coli* from Joshua Lederberg at the University of Wisconsin. As described by Kay, "these different mutant strains were central to the material culture of microbial genetics, circulating widely within its international network" (Kay 2000:206).

The completion of this move would eventually lead, not to the adding of a dimension in the representation of biological systems, but to the reduction of biological space to one dimension *only*, namely the genetic map or sequence. Three-dimensional biological space was on its way to be recast within the uni-linearity of informational space.

The lac mutations were mapped along the genome of E. coli: The ability to synthesise permease was located to the "Y" gene and that of synthesising galactosidase was located to the "Z" gene. It was discovered that the constitutive vs. the inducible character of the two genes seemed to be linked, and so this "meta-control" was ascribed to a site of its own, the "I" gene. The I - gene seemed to be distinct from the two others and it seemed to be able to turn these on and off, hence exercising a sort of meta-control. It thus seemed that there were actually two levels of genes. Whereas one level was responsible for the direct induction of enzyme synthesis, the other level would in turn regulate the actions of the first level genes. As it turned out, the I-gene was working in a different way from what had been previously assumed. This mechanism had been represented in terms of a replacement of the inducer, hence a sort of positive control. Now, however, in a move that would further expand the scope of genetic explanations by the borrowing from cybernetics and communication theory, it was represented as the removing of an inhibition (as will be seen, the articulation of this mechanism would soon be improved through the operon model).

This result came about by cross-mating two strains of the I–gene: one was constitutive for synthesis of galactosidase and permease (I-); the other was inducible (I+). "Inducible" in this context meant that the I+ strain would synthesise the two enzymes only in the presence of lactose, whereas the "constitutive" strain (I-) would synthesise both enzymes also in the absence of lactose. When crossed, the I+ strain surprisingly turned out to be dominant over the I- strain. The product of the I+ gene was then represented in terms of an inhibitory mechanism: the strain did not produce the enzymes galactosidase or permease; it produced an *inhibitor* that would repress the production of the two enzymes. The I- mutant, then, was constitutive because it was lacking this inhibitory mechanism. The regulatory mechanism of enzyme production was now relegated to one further gene operating on the I + gene in the form of a de-repressor. When galactosidase and permease were synthesised in the cell plasma,

it was actually because this de-repressor inhibited the inhibitory products of the I+ gene: a chemical movement of double negation.

These complex and technical deductions are worth mentioning for the following reason: by these movements, Jacob and Monod abstracted the genetic regulatory apparatus away from the ordinary biochemical workings of the cell and moved them into the (supposedly) closed-off space of the nucleus. A few years later, they constructed the division between *structural* and *regulatory* genes on the basis of findings like these. Here was a genetic explanation that seemed capable of answering the aforementioned problem of why genes do not act all the time. The answer was that they were switched on and of by the regulatory genes. The regulatory genes, it was figured out, worked by the two mutually constituting mechanisms of induction and repression. The structural genes, i.e. Y and Z, were structuring the information necessary for the synthesis of permease and galactosidase. This (autocatalytic) process was halted by a repressor enzyme that was determined by the regulatory gene (I). *Induction* was then pictured as the repression of the repressor. When compared to the notion of adaptation as described above, it becomes clear that the notion of nuclear interaction with the environment (the cytoplasm) had been removed from its original significance. Adaptation (induction), originally the property of an enzyme, had been reconfigured as a property of the genetic regulatory apparatus, which in turn was soon to be integrated within the *genetic program*. What this entailed was a radical reconfiguration of hereditary mechanisms, from existing in biological, three-dimensional space, to the uni-dimensional and immaterial notion of *information*. The material was separated from the immaterial, the cytoplasm from the nucleus and the biochemical from the genome (Kay 2000; Fox Keller 2002).

In this way, Crick's central dogma was both confirmed and expanded. Confirmed, because the only way that the necessary relation between nucleus and cytoplasm could be maintained went by imagining gene expression as a one-way street: information is transferred from the nucleus, but it cannot, under any circumstance, find its way back into the nucleus. Expanded, because its integration into the notion of the genetic program allowed for far more differentiated and complex analyses, notably of the whole genome as such (once again, the attempt at integrating genetics with embryology was given a spark). The notion of feedback, to take one central example, would previous to these developments be conceptualised in terms of inhibition by end-product, a biochemical equalisation in order for a system to conserve itself at a steady state under the influence of varying environmental circumstances. On this

view, the end-product, re-entering the system so as to inhibit further synthesis, still exists on a par with the other parts of the system.

According to the informational view, changes in the state of a system would also come about as a result of external influence (an inducer). But there would be no exchange of *information* taking place whatsoever: information is moving in one direction only. The nucleus issues its orders through mRNA to repression enzymes in the cytoplasm, thus switching on and off the synthesis of enzymes in the presence of the inducing substance. In this way, notions of learning and experience were relegated from the conceptual apparatus of cell mechanisms. With information going only one way: how could the cell adopt anything external to the genetic program? Monod promptly put it in the following manner:

> "The entire system is totally, intensely, conservative, locked into itself, utterly impervious to any 'hints' from the outside world. By its properties, by the microscopic clockwork function that establishes between DNA and protein, as between organism and medium, an entirely one-way relationship, this system obviously defies 'dialectical' description. It is not Hegelian at all, but thoroughly Cartesian: the cell is indeed a machine" (Monod 1971).

Last, but not less important: it was during the PaJaMa experiments that messenger RNA first turned up as a possibility on the experimental and theoretical horizon. Within a few minutes after coitus, the recipient cell would start to synthesise galactosidase. Because Jacob and Wollman had already established that recombination would take more than an hour, the synthesis could not be the result of genetic recombination, but was rather explained in terms of a direct signal, or messenger, from the nucleus to the cytoplasm. This then, would eventually turn out to be the missing link between gene and cytoplasm (mitochondria). In the 1961 May Issue of *Nature*, two papers appeared that, each from its perspective, identified the messenger RNA. During a stay at Caltech, Francois Jacob, together with Sydney Brenner and Matthew Meselson, set out to prove that the synthesis of proteins in phage was controlled through the mediation of messenger RNA attaching itself to the bacterial ribosomes. Deploying techniques developed by Meselsohn entailing centrifugation of radioactively labelled bacteria, the aim of the experiment was to show how the mRNA from labelled, phage-infected bacteria would attach to the ribosomes of the infected host bacteria. After repeated centrifugations, their hypothesis was confirmed. Elaborating on these results by similar methods, James Watson and Francois Gros also demonstrated a close (base ratio) correspondence between the templates of mRNA and DNA, and it was these results that made up the second *Nature* paper referred to above.

In 1953 Monod became director of the Pasteur Institute. Already situated at the forefront of physiological research in France as well as internationally, the institute became an excellent vehicle for his project of modernising French biology. As described by Lily Kay, social activism and experimental activity were not sharply separated in Monod's projects. He immediately took it upon himself to reorganise the Institute "completely" in terms of laboratory equipment, teaching facilities and increase of personnel. In 1936 he had held a postdoctoral Rockefeller Fellowship at the Caltech biology division of biology. He now applied to the Foundation for funding for the modernisation of the institute. The application was, as he himself described, a very ambitious one, encompassing the biosynthesis of proteins (enzymes), nucleic acids, amino acids, as well as puric and pyrimidine bases and nucleotides. Still, he contended, as the program "concentrated on the same microbiological material (E. coli) and common methodologies it would be cooperative and quite focused" (Kay 2000:204).

I have described some central aspects of what was to become the beginning of the closure of the mechanisms of heritage and development. Under the aegis of the genetic program what would serve as the object domain of the new discipline of micro-biology in the 1960s was carved out, mainly from the workings of one unicellular organism, the bacteria E. coli. E. coli itself does not undergo cellular differentiation, but this did not seem to bother Jacob and Monod in their attempts at extrapolating their findings in bacteria to other organisms: what was true of E. coli was also true of the elephant (*ibid*.).

The Genetic Program

In the (late) 1950s, enzymatic regulation and cellular differentiation were more and more frequently described in terms of feedback mechanisms, a conception taken from cybernetics and communications theory. It had been demonstrated that enzymes were produced by auto-catalysis: a self-generating mechanism also contributing to specificity insofar as it depended on the competition between different enzymes for the same resources (cf. above section). But self-generation could not proceed infinitely; something would have to stop the process before it reached catastrophic levels. This mechanism was first explained in terms of end-product inhibition, and, with the coming of cybernetics, as negative feedback. The discussion went, as before, about the site and nature of these regulations: was it pure biochemistry relying on the cell as a whole, or was it genetic, hence also exclusively nuclear? David Nanney compared

these two different views of cellular mechanisms to a democratic versus a totalitarian state. In the democratic version, "The Steady State", feedback models would serve as general explanations of a wide range of cellular mechanisms tending towards steady states. On this conception, stability is not owed to one kind of molecule only, "but to the functional relationships of these molecular species". In the totalitarian version, feedback became the servant of the nucleus (Nanney 1957)[45]. One year later, the totalitarian version would be strengthened within the frames of an informational paradigm and given its most powerful articulation in Francis Crick's Central Dogma of molecular biology:

> "…once information has passed into protein it *cannot get out again*. In more detail, the transfer of information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the *precise* determination of sequence, either of bases in the nucleic acid or of amino acid residues in the protein" (Crick 1958).

The conception of the genetic program was introduced by Jacob and Monod at the 1961 Cold Spring Harbour Symposium. The main purpose of the new conception (borrowed from computer science) was to extend the results from the studies of enzyme synthesis in E. coli to the study of embryological development[46]. This was carried out through a bold leap that would unite many of the findings described during the last pages and explain them within the new conception of the genetic program: the repressor, negative feedback, the messenger RNA, and, one last (f)actor that has yet to be mentioned, the operon. As already pointed out many times: Early articulations of the gene seemed ill-fit to describe both heredity and development at the same time. Even though the hereditary mechanism had been elucidated through the structure of the double helix, the question still remained as to how differentiation came about, and how it could be that genes were not acting all at the same time. Even though this had been answered in part by the division into regulatory and structural genes, that was hardly satisfactory. It had been established that the regulatory genes switched the structural genes on and off. In that way, both the rate and the structure of protein synthesis had been explained. But what about the regulatory genes? Who or what was in charge? And how was the action of the regulatory genes integrated within the organism as a whole?

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[45] Interestingly, Nanney also conceived of two versions of the "totalitarian molecule". The simple version corresponds more or less directly to the central dogma. The other, refined version, would also recognise that "organic specificity be a function not only of the intrinsic capacities of the system, but also of the environmental circumstances" (Nanney 1957).

[46] Jacob and Monod had in the meantime, triggered by a reflective leap of Jacob's, established that immunity in bacteria was depending on the same repressive mechanisms as in enzyme synthesis (Kay 2000).

The genetic program was designed to provide molecular biology with an analytical basis for relating the activation of various genes to the development of the organism as a whole. Although the identification of the chemical basis of these processes may have done damage to the notion of gene action as posed within the old, biochemical paradigm, in which specificity was pictured as having a material basis[47], this potential was soon regained within the new paradigm of information**.**

It was now recognised that specificity was due to nucleotide sequence, and that this in turn could be represented in non-material terms, as code or as information[48].

This was not an outcome of biological experimentation *per se*. Where the basic metaphors had earlier been provided in terms of human agency, at the threshold to the age of information the genome would be described by metaphors taken from computer science. Hence, the genome sequence was compared to the computer programs of the day, in which information would be loaded onto a magnetic tape, issuing its order in binary codes lined up in a uni-directional sequence as the tape was read off. The regulatory and structural genes were seen to operate in a manner similar to this. Also they were issuing binary orders, switching protein synthesis or other genes on and off (Fox Keller 2002).

By 1961 it had been established that the regulatory genes worked by issuing orders through messenger RNA. It had also been established that the mRNA would translate into proteins that in turn would act as de-repressors upon the inhibitory mechanisms of the structural genes. In that way, the regulator gene induced protein synthesis. The specific site for this exchange of information between the regulatory and structural genes was now conceptualised in terms of the *operon model*. The operon was portrayed as the site in which the instructions from the regulatory genes are carried out; a complex of regulatory elements and structural genes (Fox Keller 2000). On this view, the synthesis of proteins and enzymes was no longer to be seen as regulated in terms of end-product inhibition, in which regulation takes place solely between enzymes within the same autocatalytic pathway; synthesis was now to be regarded as determined by the regulatory genes, so-called "allosteric inhibition". Theories of enzyme synthesis were not wrong, but they did not get to the specific sites through which differentiation was controlled. Enzyme synthesis was thus dismantled from ordinary

[47] Notably through the template hypothesis.
[48] For the notion of the genome as a code to be deciphered, see (Kay 2000).

enzymatic activity taking place at the level of the cell, the former now being regarded as genetically determined. The proteins issued by the regulatory genes work by directing synthesis, but do not themselves take part in the synthesising process. This order was now invoked to explain the genetic determination of cellular differentiation; explanations on the level of ordinary enzyme synthesis being as it were insufficient for the job (Fox Keller 2002), 155. One important reason for so doing was the urge to move from models of enzyme synthesis in bacteria to the organisation of higher organisms.

Initially, this move entailed an *Aufhebung* of explanations of cellular mechanisms onto the level of genetic regulatory mechanisms in which the cellular is subordinated to the genetic. But in one further move this division itself was now moved onto a different, genetic level.[49] Cellular differentiation displays both stability and change at the same time: some phenotypical traits are conserved for centuries whereas others undergo change. The problem faced by Jacob and Monod was how to explain this phenomenon from the point of view of the genome. If the operon model was to go along with Crick's central dogma, according to which conservation is maintained genetically, it was necessary to show that the genetic material did not itself undergo any changes during the course of evolution. The notions of cellular versus genetic, activity versus synthesis, were now recast within the language of information in terms of conservation and change. As such, the question no longer came to hinge upon the biochemical language of the old days: "The very terms of the new configuration reflect a shift from the discourse of biochemistry (and also, though less conspicuously, from the taxonomy of classical genetics) to the language of molecular biology, and specifically, to the language of Francis Crick's central dogma" (*ibid*., 164).

The operon model, it was argued, provided the means for the proper analysis of informational change and conservation. By switching on and off the structural genes, the regulatory genes would provide for both conservation and change of gene expression. The regularities and changes thereby entailed would reside in the genome itself, or, more specifically, in the genetic program. One pressing task, therefore, resided in deciphering the "code" according to which gene expression was regulated: "The unity of cellular mechanisms across species divides would hold if the code were shown to be universal" (Kay 2000:233).

[49] Indeed; insofar as the term *Aufhebung* is pertinent description of this move, it is Luhmannian rather than Hegelian: One difference being replaced by another difference, this time on a higher analytic level. This hardly comes as a surprise, as Luhmann takes his conceptual apparatus from some of the same sources as Monod. But from the level of cellular differentiation to that of social differentiation, there is quite a leap.

What was thereby presupposed was the status of the genetic program as the final unit responsible for development. Indeed, if it was true that the genome did not undergo change and that it determined differentiation from the very beginning of life, the genome had to be pre-programmed so as to carry *all* the essential information required during ontogenesis, the development of the organism. The notion of teleology, for many years relegated to the periphery of biological discourse, now reappeared in its middle. To be sure, teleology did not reappear in Aristotelian or Lamarckian terms, in which the purposeful interaction of the organism with its environment takes place as an open-ended process. The concept of teleology was recast as *teleonomy*, in which the purpose of the organism as a whole was inscribed in the nucleus *qua* genetic program from the very beginning.

Furthermore: With the coming of the operon model, it needed no longer be presupposed that genes act. Now they were depicted as activated by other genes possessive of a regulatory function only. But this, says Fox Keller, merely served to transpose the problem onto a different level:

"It was of course understood that, in order to do their job and turn the structural genes on and off, regulatory genes themselves needed to be activated, but this fact seemed to present no impedance whatsoever to the new construction. Part of the reason for this is already suggested by the legacy of so long a tradition of agentic discourse in genetics, and by the persistence of ingrained habits of thinking and talking that maintained the capacity to act, control, or to govern as an inherent property of the gene, even after the gene had been recognised as no more than a chemical molecule, and a relatively inert one at that" (Fox Keller 2002:138-139).

In this way the discourse of agency was replaced: from the level of the single gene to that of the genome, which was in the end controlled by the genetic program. Finally then, Bernard's "invisible guide" had been given an articulation within the language of molecular biology. But the computer metaphors had its obvious limitations. Who had "programmed" the genome? And how was it supposed to be understood that the program "acted"?

Stabilising the genetic code

"it is difficult to eliminate the possibility that the minute amounts of protein that probably remain attached to DNA, though undetectable by the tests applied are necessary for activity…There is accordingly some doubt whether DNA is itself the transforming agent, although it can be regarded as established that DNA is at least part of the active principle", Alfred Mirsky (1951), quoted from (Fruton 1999:441).

Lily Kay describes the year 1961 as decisive to the coding problem. In this year, the search for the genetic code left its "formalistic" phase and entered upon a more "materialistic" path. By this, she means that the search for the principle correlating nuclide acid synthesis with amino acid synthesis came to rely less upon the efforts of cryptographs, communication theorists, physicists and mathematicians, and more upon biochemical "bench-work" proper. Catherine Waldby has criticised Kay for relying upon too simplistic categories in evaluating this shift; from "bad", militarised research to "good" biochemistry (Waldby 2001). But we do not have to follow Kay's arguments all the way: for the present purpose, it will suffice to note that the direction of research was changed quite suddenly and unexpectedly by the success of a biochemical approach. In a somewhat looser sense than that intended by Kay: research took a dynamic turn, away from abstract and structural approaches towards functional, biochemical ones.

In 1958, Francis Crick articulated the problem in terms of two general principles: the sequence hypothesis and the central dogma. The sequence hypothesis stated that "the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and that this sequence is a (simple) code for the amino acid sequence of a particular protein" (Crick 1958). He further envisioned two possible paths to the discovery of the correlating principle between the two. One went by way of biochemical analysis, the other would deploy more "abstract arguments". Although highly up-dated on both fronts, it seems fair to state that Crick's preferences lay more on the abstract and structural side than on the experimental and dynamic. The works on the structure of DNA with Watson from 1953 clearly displayed this, and his close connection to the so-called "RNA Tie Club", significantly as articulated in the works of physicist George Gamow, was one further fact about the matter. Hence, after explaining the biochemical issues involved, Crick stated that:

> "So much for biochemical ideas. Can anything about protein synthesis be discovered by more abstract arguments? If, as we have assumed, the sequence of bases along the nucleic acid determines the sequence of amino acids of the protein being synthesized, it is not unreasonable to suppose that this inter-relationship is a simple one, and to invent abstract descriptions of it. This problem of how, in outline, the sequence of four bases 'codes' the sequence of the twenty amino acids is known as the coding problem. It is regarded as being independent of the biochemical steps involved, and deals only with the transfer of information. This aspect of protein synthesis appears mainly in the more sophisticated sciences. Most biochemists, in spite of being rather fascinated by the problem, dislike arguments of this kind. It seems to them unfair to construct theories without adequate experimental facts. Cosmologists, on the other hand, appear to lack such inhibitions" (*ibid*.).

Breaking the code

Marshall Nirenberg must have been such an experimenter as referred to by Crick: a biochemist with a "fascination for the coding problem". Nirenberg became a research fellow at the Bethesda NIH (National Institute of Health) laboratory in 1957. The NIH research facilities were known to be at the apex of biological research, albeit not in the fields of molecular biology or genetics. Having as it was a long established tradition in biomedicine the NHI remained conservatively based upon biochemistry rather than jump the new disciplines. This also carried with it a certain hostility towards these disciplines, as famously articulated in Erwin Chargaff's notion of molecular biology as "biochemistry without a license". The general direction of the argument was that the theories of the molecular biologists were speculative and underdetermined by experimental evidence (Kay 2000). However, if the difference between the two disciplines was sharp, it should be added that it would also turn out a very productive dialectic. Just as Crick was updated on the latest in biochemical research, so Nirenberg, originally working in enzymology, was familiar with the works of Jacob and Monod. He knew about the latest in phage research and biochemical genetics, and he knew of the different approaches to the coding problem put forth by Crick, Gamow and the RNA Tie Club (*ibid*.).

As is getting clear along with the growing evidence from the Human Genome Project: the cell is indeed a complex thing: "We know about molecules; we know about cells and organelles; but the stuff in between is messy and mysterious" (Ball 2003). If this is the case today, then it must certainly have appeared no less so to the biochemists trying to trace the movement of tRNA through the cell in the late 1950s/early 1960s. As retrospectively stated by Francis Crick:

> "The central dogma was put forward at a period when much of what we now know in molecular genetics was not established. All we had to work on were certain fragmentary experimental results, themselves often uncertain and confused, and a boundless optimism that the basic concepts involved were rather simple and probably much the same in all living things" (Crick 1970).

There is no direct pathway to cellular mechanisms, one have to proceed by the use of "genetic tricks" (Watson, Tooze et al. 1983). One way of breaking open the black box of the cell and getting to the underlying biochemical pathways went by destroying the cell membrane so as to be able to intervene directly with the (known) factors of the system: nucleic acids and enzymes, ribosomes, ATP and GTP ("molecular fuel") and amino acids. The cell was broken

down into its constituent chemical parts by running it through a blender, and a number of amino acids were added, one of which was radioactively labelled. Paul Zamecnik, with whom Crick kept in close contact, demonstrated through such a "cell-free system" that proteins were formed through the synthesis of RNA with amino acids in the ribosomes. Moving from the study of rat liver cells to E. coli, he further optimised the system in terms of a higher incorporation of amino acids into protein (Rheinberger 1997). For the purposes of decoding, however, there remained a crucial problem: if the system was to yield the exact relation between the nucleotide sequence and the proteins, something had to be known about the nucleotide sequence. Without knowing the input of the system, the output also remained mysterious in terms of genetic explanation; the essential information was lacking, and it was hard to envisage a way of getting to it.

One step forward was made by Tissière, who demonstrated the inhibitory effect of the enzyme DNAase on the synthetic activity of the cell-free system. Except from providing a useful experimental tool, this also went a long way in proving the role of RNA as an intermediate messenger between the nucleotide sequence and the protein. DNAase works on DNA by chewing the sequence into pieces (as does RNAase on RNA). And so it was deduced that since the "action" of the DNA had been halted it had also halted RNA synthesis. This enzymatic mechanism, then, offered a way of freezing the system so as to facilitate observation on different stages of protein synthesis.

It was the improvement of the techniques working with cell-free systems that would eventually lead Nirenberg and his co-worker, Heinrich Matthaei, to break the genetic code. After working for a long time just to stabilise the system for their purposes, they were able to report the discovery of a new type of RNA, namely messenger RNA[50]. One reason why mRNA was discovered later than tRNA and rRNA was its unstable and short-lived condition. Shortly after transcription, mRNA is destroyed by the enzyme RNAase. But it was also this fact that allowed for its discovery. When RNAase was added, protein synthesis would stop, and so it was inferred that there had to be a "ribosomal RNA", which was shortly after given the name of mRNA (Kay 2000). The experiment that would eventually "break the code"

[50] The existence of the messenger had already been indicated by the PaJaMa experiments at the Pasteur Institute and by experiments conducted by Watson and Gros at Harvard. Gradually it became known to wider circles: "The concept of the messenger was obviously "in the air" in these days. It was bandied about in conferences during the fall of 1960" (Rheinberger 1997:213).

followed as a systematic testing out of different amino acids, synthetic as well as endogenous, as inputs into the system to discover if any acid of known composition would perform the role of the messenger. By feeding into the system radioactively labelled poly-uridylic acid (Poly-U) and phenylanaline, Matthaei observed high degrees of the protein polyphenyalanine on the Geiger counter. The result seemed incontestable: the amino acid Poly-U coded for the protein polyphenyalanine (*ibid*.), and hence a definite relation was established between nucleic sequence and protein.

In 1958, Francis Crick wrote that:

> "Once the central and unique role of proteins is admitted there seems little point in genes doing anything else. Although proteins can *act* in so many different ways, the way in which they are *synthesized* is probably uniform and rather simple, and this fits in with the modern view that gene action, being based upon the nucleic acids, is also likely to be uniform and rather simple" (Crick 1958).

Out of all the amino acids existing in nature, a limited number had been singled out as the "magic twenty": "…only about twenty different *kinds* of amino acids occur in proteins, and…these same twenty occur, broadly speaking, in *all* proteins, of whatever origin – animal, plant or micro-organism" (*ibid*.). In 1953, following Erwin Chargaff's demonstration of nucleotide base composition gathered from a number of different species to be (almost) uniform, Watson and Crick had also established the relation between the two corresponding nucleotide base-pairs:

> If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms...it is found that only specific pairs of bases can bond together. These base pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine)...if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined (Watson and Crick 1953).

Here, then, was how Crick and his colleagues in the RNA Tie Club came to perceive of the problem complex: primarily as a relation between numbers, frequently also supplied by the relations between linguistic entities like letters, words, sentences and so on: "This problem of how, in outline, the sequence of four bases 'codes' the sequence of twenty amino acids is known as the coding problem. It is regarded as being independent of the biochemical steps involved, and deals only with the transfer of information" (Crick 1958). What this suggested to Crick and his colleagues, was that there had to be some limitation, or some definite rule

governing the arrangement of the nucleotide bases. The already mentioned sequence hypothesis was the concrete outcome of this state of affairs: "…the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and …this sequence is a simple code for the amino acid sequence of a particular protein" (*ibid*.). In other words: what the decoders were looking for was the basic unit of information transfer. This would have to be restricted in two directions simultaneously: first, it was the question of the *order* of the base pairs. Second, the *size* of the coding unit: how many bases did it take to make up one unit? Was it double, triple or quadruple, or was the number even higher? And, supposing the correct number had been established: how was the code actually *read*? (Kay 2000).

In this manner, the problem of biological meaning was further conceptualised in terms of information. As already seen: for Crick the coding unit came to be seen, somehow inconsistently, as separated from its biochemical basis. Biological meaning was given indiscriminately through the sequence of information, and not through the chemical agents. Following Gamow, the coding problem typically revolved around different possibilities given by the two numbers of four and twenty. Given the four bases, a two-base unit (codon) would add up to 16 combinations (4 x 4). But this number would be insufficient to account for the specificity of the twenty amino acids, and so 4 x 4 x 4 seemed a more likely alternative, according to which the possible combinations amounted to 64. These kinds of formalistic approaches led many biochemists to look with some suspicion upon the abstract musings of molecular biologists, as for instance given in Joseph Fruton's dismay with the "hypnotic power of numerology" (Fruton 1999:461).

Still, "numerological" and informational features also found their way into the thinking of Nirenberg and Matthaei, and along with them also into the conceptual apparatus of a new generation of biochemists: "informational macromolecules" came to be seen as the bearers of genetic specificity (Kay 2000). Previous to the experiment that would finally yield a glimpse into the genetic code, they had been guided by the idea of a triplet code, an idea already nurtured for some time by Crick and Gamow (*ibid*.).

The idea of the triplet code was clearly articulated in an important paper by Crick and colleagues, published only weeks after Nirenberg and Matthaei's publication of their discovery: "A group of three bases (or, less likely, a multiple of three bases) codes one amino acid" (Crick, Barnett et al. 1961). The paper also stated that "The sequence of the bases is

read from a fixed starting point. This determines how the long sequences of bases are read off as triplets" (*ibid*.).

Following the publications of Nirenberg and Matthaei in 1961, the decoding work changed its direction, and a greater number of biochemists entered the race to complete the work on the code by the use of cell-free systems. In 1960, the mounting evidence for the existence of mRNA had suggested to Severo Ochoa (New York Academy of Medicine) that he deploy synthetic polynucleotides as messengers into the system, and that this procedure may eventually lead to the desired goal of breaking the code. In that way, says Kay, mRNA became simultaneously an epistemic and a technical thing, serving both as a probe into the workings of the system and an entity to be highlighted for its own sake; mRNA was involved in a dialectic of representing and intervening, the final aim of which was the cracking of the code (Kay 2000).

Disappointed by the priority of Nirenberg and Matthaei's discovery, Ochoa now made the completion of the code the main objective of his laboratory, and he did this by the continued use of mRNA. First, its role was affirmed through the observation that its insertion into the *E. coli* system would increase the rate of the synthesis of Poly-U into phenylalanine. Hence, Nirenberg and Matthaei's result was also affirmed. He then turned to the use of mixed polynucleotides (heteropolymers), observing that more amino acids than one were generally involved in protein synthesis. In a 1962 article published in the *Proceedings of the National Academy of Sciences*, they were able to increase the list of amino acids involved in protein synthesis to eleven, a publication that was soon after followed up and (partly) affirmed by a list of fifteen from Nirenberg and his colleagues at the NIH (*ibid*.). The article, "Ribonucleotide Composition of the Genetic Code", also served to put the possibility of a triplet code on firmer experimental ground.

Although the nucleotide composition of the "magic twenty" amino acids involved in protein synthesis were being rapidly determined, Crick's coding problem remained unsolved. How to decide the size and sequence of the basic unit, increasingly known as the "codon"?

One main problem was posed by the so-called *degeneracy* of the code: more than one coding unit seemed to be involved in the synthesis of most amino acids. For instance: today we know that the amino acid Proline is coded for by CCU, CCC, CCA and CCG. But if the sequence

of, let's say, CCU is not known, it can only be represented in terms of its composition, as C_2U. This unit may also turn up as CUC, which codes for Leucine and not Proline. Gobind Khorana of the University of Wisconsin set out to clear the field by obtaining completely defined sequences of ribopolynucleotide messengers (mRNA) as a starting point for mapping. This turned out a difficult task, however. DNA synthesis had been some years in the coming and so was fairly well developed, but the same could not be said about chemically induced RNA synthesis. He therefore turned to DNA synthesis, and in 1963 he succeeded in synthesising a DNA polymer comprised of the two bases A and T, which would in turn transcribe as A and U bases in the RNA chain. Following this success, he continued to synthesise di- and tri-nucleotides for decoding purposes (Kay 2000).

In the NIH laboratory, Nirenberg and his assistant Philip Leder were occupied elaborating techniques that would complete the decoding process. In 1964, they devised the so-called "triplet binding assay", which thrived on the discovery of the role of tRNA and amino acids in protein synthesis: ribosomes, the "protein-synthesising machinery" of the cell, attach to RNA triplets only in the presence of an aminoacyl-tRNA complex. A tRNA complex is a tRNA linked to a specific amino acid. tRNA serves to bind the mRNA codons to their specific amino acids so as to unite them into protein chains. In this way, the original nucleotide sequence is retained. The tRNA unit was baptised the "anti-codon", as it corresponded exactly to the codon sequence found in mRNA. In 1965, Robert Holley and his research group at Cornell had managed to map the sequence of Alanine tRNA in yeast. They also managed to determine the Alanine codons: GCU, GCC, GCA and GCG.

The step that would finally lead to the completion of the genetic code took advantage of the discoveries of Holley and Khorana: if the composition of the amino acid that was incorporated was known, and if the sequence of the anti-codon (in tRNA) was known, then the sequence of the mRNA could also be determined. By inserting one of Khoranas artificially synthesised trinucleotides into the system, they would not have to deal with the problem of how to isolate one codon from the very complex sequence of ordinary RNA. Furthermore, because the sequence of the tRNA was determined, the problem of the direction was also solved. In this manner, while the mRNA would give the composition and the tRNA would give the direction of the sequence, the reading mechanism (translation) of protein synthesis was established. Because Khorana had obtained a complete set of trinucleotides (64), the code could finally be completed (*ibid*.).

In this manner, they were able to read off the translation process taking place in the cell: In a paper from March 1965, Nirenberg and his colleagues reported that:

> "Nucleotide sequences of RNA codons have been investigated recently by directing the binding of C14-AA-sRNA [the amino-acid complex] to ribosomes with trinucleotides of defined base sequence. The template activities of 19 trinucleotides have been described and nucleotide sequences have been suggested for RNA codons corresponding to 10 amino acids. In this report, the template activities of 26 additional trinucleotides are described and are related to the general nature of the RNA code" (Nirenberg, Leder et al. 1965).

Through Holley's elucidation of tRNA, it also became possible to explain the degeneracy of the code. Because of the spatial folding of the molecule, the anti-codon site is bent, and so strict specificity is only obtained by the first two bases, whereas the third base may vary. Crick termed this the "wobble" of the code (Kay 2000). In 1968, Khorana, Holley and Nirenberg shared the Nobel Prize "for their interpretation of the genetic code and its function in protein synthesis" (The Nobel Prize Organisation 2005).

Before I continue the story with some considerations of a more institutional character, I will make a brief pause to relate this last section to what has earlier been stated about gene action and the genetic program. As described, the biochemical turn was also inspired by more abstract reasoning, as provided by Crick, the RNA Tie Club, and by Jacob and Monod. Of specific significance was the re-articulation of gene action within the linguistic framework of the information discourse, in which, as we have seen, genetic properties came to be separated from the material biochemistry involved. What the biochemical turn provided, was a way of getting to the concrete structure of gene action, without thereby sacrificing the potential inherent in the information discourse. Finally, the structure of the gene had also yielded its function (Fox Keller 2000). Obviously, this provided molecular geneticists with a strong tool also for the sake of concrete intervention with genetic processes. And, as will shortly be seen, genetic engineering and recombinant DNA technology was right around the corner. However, what the biochemical turn did not yield was the (ontological) order of the genes. What kind of genes are there? How do they interact among themselves, and how do the complexes of different genes affect cellular growth and differentiation?

The RNA codons

	Second nucleotide				
	U	**C**	**A**	**G**	
U	UUU **Phenylalanine** (Phe)	UCU **Serine** (Ser)	UAU **Tyrosine** (Tyr)	UGU **Cysteine** (Cys)	**U**
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	**C**
	UUA **Leucine** (Leu)	UCA Ser	UAA **STOP**	UGA **STOP**	**A**
	UUG Leu	UCG Ser	UAG **STOP**	UGG **Tryptophan** (Trp)	**G**
C	CUU **Leucine** (Leu)	CCU **Proline** (Pro)	CAU **Histidine** (His)	CGU **Arginine** (Arg)	**U**
	CUC Leu	CCC Pro	CAC His	CGC Arg	**C**
	CUA Leu	CCA Pro	CAA **Glutamine** (Gln)	CGA Arg	**A**
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	**G**
A	AUU **Isoleucine** (Ile)	ACU **Threonine** (Thr)	AAU **Asparagine** (Asn)	AGU **Serine** (Ser)	**U**
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	**C**
	AUA Ile	ACA Thr	AAA **Lysine** (Lys)	AGA **Arginine** (Arg)	**A**
	AUG **Methionine** (Met) or **START**	ACG Thr	AAG Lys	AGG Arg	**G**
G	GUU **Valine** Val	GCU **Alanine** (Ala)	GAU **Aspartic acid** (Asp)	GGU **Glycine** (Gly)	**U**
	GUC (Val)	GCC Ala	GAC Asp	GGC Gly	**C**
	GUA Val	GCA Ala	GAA **Glutamic acid** (Glu)	GGA Gly	**A**
	GUG Val	GCG Ala	GAG Glu	GGG Gly	**G**

The RNA Codons and their corresponding amino acids, reprinted from Kimball's Biology Pages (http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/)

As described, Jacob and Monod had already served the conceptual apparatus through which gene action would be recast: the genetic program, acting on the scale of the whole genome, interaction taking place at the site of the operon. But, in moving from the single gene to the whole genome, it becomes clear that the function of the gene had not been entirely elucidated through its function. Even though the correlations between the different nucleotides and the amino acids were known, the question of genomic structure remained wide open. It would also soon become clear that the operon model did not apply to biosynthesis in higher organisms, where the process is altogether more complex. Gene expression is regulated mainly (but not only) by the rate of translation of DNA into different RNAs, processes that are in turn triggered by different mRNA polymerases and the promoter (Winter, Hickey et al. 2002).

The operon model and the conception of the genetic program did indeed expand the scope of genetic explanation greatly. But at the same time it must be clear that it challenged the simplicity of the Crick model. Hence, Fox Keller describes the distinction between structural and regulator genes as "the first wrinkle on the face of the central dogma" (Fox Keller 2000), 55. And, indeed, this was only the beginning of the exploration of the many genes there is and of the many functions they may have. I will have some more to say about this at a later stage. Now, something more must be said about the institutional setting of the 1960s and the transition to the phase of genetic technology.

Nirenberg and his colleagues at the NIH were regarded as outsiders in the de-coding competition, and when they somehow unexpectedly struck gold, many established and well-known de-coders would describe their results as a strike of luck. Matthaei and Nirenberg, however, denied any such allegation, and they claimed their code-breaking experiments to be the result of hard, systematic work designed to achieve the breaking of the code and nothing else. The fact that other researchers, significantly Severo Ochoa, were steering in the same direction indicates that this was indeed the case. Furthermore: if one takes a look at the major investments made in basic research in the post-war period, the results seem even less random. The NIH was at the centre of a fast-growing governmental program designed to stimulate research on a broad scale. We have seen that in the pre-war era, research funding was primarily a matter of private patronage, like that exercised by the Rockefeller Foundation or by the universities themselves. But with the coming of the cold war, huge amounts of state

money were poured into weapons and space research, and science in general profited from its potential for the "industrial-military complex".

Along with these developments, investments in biomedical research grew proportionally. In part, the increase came as a result of the general attempt of the Truman Program to strengthen health and social conditions. But it was also stimulated by powerful lobbying groups, such as the Lasker Foundation and the American Medical Association, to direct research towards the fight of disease, significantly towards cancer research (Wright 1994). The NIH came to be seen as the main promoter in these efforts, both in terms of performing actual research and as an instrument for allocating research funds on a national basis. Between 1945 and 1968, investments grew steadily, from 2.8 million dollars in 1945 to more than 3 billions in 1968 (numbers in 1982 dollars) (*ibid*.). Come the 1960s, the state financed network of biomedical research was spread among universities and research facilities all over the USA, and the NIH formed its organisational and scientific basis. With reference to the classical physiological research paradigm, it may seem as if this research came close to fulfilling the Bernardian ideal: providing a basis for curing disease through a broad program of basic research. However, the ideal of "pure basic research" is hard to achieve, not least because it requires economical resources that necessarily stem from sources that do not and can not share in the scientific ideal of disinterestedness:

> "The prevailing view within the biomedical research community was that its primary mission was the development of a scientific basis for modern medicine through progress in understanding basic biological processes. On the other hand, politicians mindful of the political mileage to be made from "breakthroughs" in the control of disease, and the pharmaceutical industry, hoping to be given new technologies and new products, emphasized the rapid achievement of cures for major diseases" (*ibid*., 27).

No doubt, the research carried out at through the NIH network in the 1960s was of a very high quality. In a 2005 interview, Marshall Nirenberg regrets the contemporary climate of strong external pressures upon young researchers to conform to existing, safe lines of research, hindering them from embarking on bold theorising or experimentation, and he recalls the conditions given to him in his youth as exemplary (The Nobel Prize Organisation 2005). But for a number of reasons, the strong growth in the research budgets could not continue. Susan Wright mentions the Vietnam War as one obvious drain on the state budget. But there were others as well: first and foremost, the growth rate of research funding had been exceptional, and sooner or later it would have to adjust to the larger balance of ins and outs on the budget,

and it would have to be defended against other priorities. This could only be done by pointing to pay-backs from science to society in terms of health improvement or industrial utility. In itself, this pointed towards a greater selectivity of funding: Research had to be justified with regard to utility factors in order to legitimise itself politically and economically. This tendency was also strengthened by the increasing need for competing on the international arena, scientifically and economically (a tendency that itself was instigated largely by US economy and politics in the post war era). Hence, even though the radically increased funding of research produced scientific results of high quality, the NIH tree could not continue to grow into the heavens. Furthermore, as illustrated by Nirenberg's regrets mentioned above, the astonishing results achieved by him and others came at a price: Whereas pre-war funding had been a matter primarily to be settled between the single researcher and his/her university, now the single researcher had been enrolled in a network of increasingly bigger research groups competing for resources with strong connections to the political, industrial and economical arenas. Through this tendency, a different type of scientist was also in the coming, namely the one in possession of "the qualities of managers and entrepreneurs" (Wright 1994:30).

The situation was not helped by the fact that molecular biology, so far, had fostered no practical applications of significance. It continued to be an experimental, though "highly promising" discipline. This, however, was soon about to change.

Recombinant DNA technology

Perhaps within the lifetime of some of us here, the code of life processes tied up in the molecular structure of proteins and nucleic acids will be broken. This may permit the improvement of all living organisms by processes which we might call biological engineering

Edward Tatum, Nobel Lecture, 1958

In the early seventies technical and scientific developments took place that promised to bring molecular biology closer to the worlds of practical application, and, at the same time, closer to the study of gene expression in higher organisms. The new technologies took advantage of a number of organisms well studied during the early days of molecular biology and deployed

newly discovered enzyme actions for new modes of intervention. In the years to come model organisms originally used to represent gene action would themselves be transformed from epistemic to technical things and turned into "molecular factories".

Early experiments on the (cloning) mechanisms that would render such technologies possible did not themselves aim directly at industrial applications, but were primarily directed towards the regulation of gene expression and the understanding of cancer at the molecular level. Paul Berg of the Stanford University Medical School investigated the actions of tumour viruses (one was the SV40), the final aim of which was the understanding of cancer development. But it was also a way of getting at mechanisms of gene regulation in higher organisms, and so the project was interesting from more than one perspective. The dialectics of basic and applied research alluded to above was exerting its effects: Funded by the NIH and the National Cancer Institute, Berg's project was well situated within the general trends in research policy of the time. And so the members of his research group were well aware of the industrial potentialities involved as well as the implications for basic research (regulation of gene expression). Many things hinged on the success in making bacteria express the genes of higher organisms. Hence, says Susan Wright, Berg's project constituted and was constituted by a definite "duality of purpose" (Wright 1986).

For almost thirty years, prokaryotes like E. coli had been used to represent genetic mechanisms in higher organisms. Following the breaking of the code by Nireneberg and his colleagues, it had been demonstrated that the code applied (almost) universally, that is, gene expression would take place following the table of nucleotide triplets and their corresponding amino acids (see above). This being the case, there should be little reason why the simpler, prokaryote organisms should not also be able to express the DNA of higher organisms, thereby producing hormones, enzymes, proteins or other physiologically or industrially important substances. Or, on a more basic level, the resulting hybrid organisms could serve as probes into the regulation of gene expression in higher organisms.

It should be noted how "primitive" these early studies of the genes and genomes of higher organisms really were, and what kinds of difficulties the researchers were up against. In 1971, when the first experiments on DNA recombination started, it was only two years since the first single gene had been isolated. The gene in question did, of course, belong to E.coli, in which it coded for the expression of the *lac* operon (Shapiro, Machattie et al. 1969). It would

last until 1974 before Brown and Sugimoto succeeded in isolating a "gene" (5S DNA) from a higher organism, the frog *Xenopus mulleri*. Hence, back in 1971, getting to pure DNA had proven notoriously difficult, and the possibilities for studying gene regulation in higher organisms were poor. The problem was not least due to all the *proteins* of the chromatins in which the DNA of higher organisms is coiled. What was all that protein doing there? Today, it is recognised that also chromatin regulates gene expression (Felsenfeld and Groudine 2003).

The way out of this dilemma went by introducing new model organisms, namely animal viruses, to represent gene expression in higher animals (Watson, Tooze et al. 1983). These viruses, like SV40 or polyoma, came in handy for a number of reasons. They posited small genomes similar to those found in bacteria (hence a strong element of familiarity), they would recombine willingly in animal cell cultures, and they could easily be labelled by radioactive isotopes (*ibid*.). Somehow ironically, since human genes could not be singled out, they also could not be studied genetically. There was no direct way of ascribing genes to our genes!

Early studies of gene expression in higher organisms had to take advantage of what was known and could be handled experimentally. Messenger RNA was one such indirect way of getting to DNA, and so research was directed towards cells in which mRNA existed in abundance. One organ that was particularly well-suited, both because of the easy access it provided and because it had been well studied almost since the beginning of biochemistry, was blood. Haemoglobin and immunoglobulin mRNA were welcoming targets (*ibid*.). The reason why I mention this here is that the blood is one typical "model organ of the human physiology", and the diseases of the blood system would prove valuable "model diseases" in the years to come. Biological thinking is based on the use of models of many different kinds, and the point is of some relevance for the discussion of the universality of biological representations and interventions.

As for the possibility of genetic intervention into human physiology: Taking for granted the present state of knowledge, stating that there is somewhere between 20 and 25 000 genes in the human genome (Coghlan 2004), it goes almost without saying that a lot was in the dark. The main significance of recombinant DNA technology would be that it allowed for the isolation and cloning of definite segments of DNA. Hence, in 1971 the question as to how the different genes of the genome relate to each other, not to say how the genome relates to protein structure, could not yet be posed in any meaningful manner.

In 1968, Meselson and Yuan had conducted experiments to investigate the action of bacteriophage on two different strains of E. coli (Meselson and Yuan 1968). During these experiments, they discovered a peculiar thing about the two strains, namely their ability to protect themselves from foreign substances by discriminating between their own DNA and that from other organisms. This was achieved by the marking of the own DNA with a specific methyl group (methylation), the absence of which singled out DNA as foreign. But the really interesting aspect lay in the discovery of the thereto connected protective mechanism: specific enzymes that would serve to cut the foreign DNA into pieces, thereby rendering it harmless. These were named restriction enzymes, or restriction endonucleases, and they would play a major role in the recombinant DNA technologies that were to come. Up until then, different DNAses had been attempted used for the cutting of exact fragments of DNA sequences, but results were meagre. These DNAses did not display the required sequence-specific action and so the results had been too inaccurate to go on with (Watson, Tooze et al. 1983).

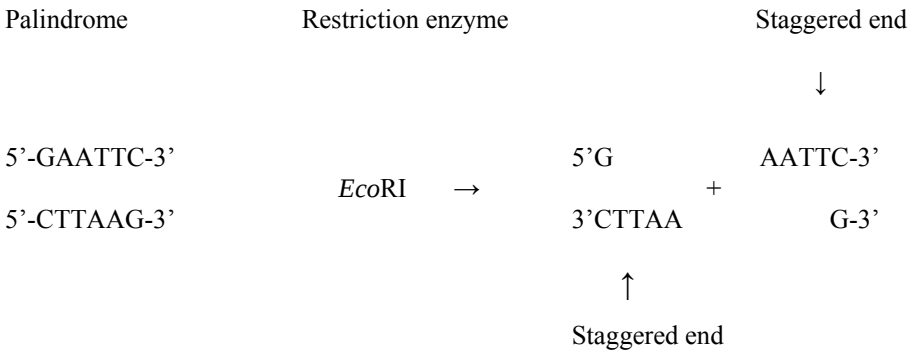
The strategy developed by Jackson, Symons and Berg was to use the phage Lambda as a vector for introducing DNA from the SV40 virus into a host culture, *E.coli*, where it would replicate. Both lambda and SV40 DNA are circularly closed, and so they had to be cleaved prior to synthesis. Such an operation had not been possible until the discovery of the restriction enzyme endonuclease. Treatment with the enzymes terminal transferase and lambda exonuclease modified the two terminis of DNA by the removal of parts of the 5' regions and the adding of complementary nucleotides to the 3' end. Next, the two DNAs were annealed (joined) to form a new circular structure and finally they were treated with E. Coli polymerase, ligase and exonuclease. The result was a hybrid molecule, containing "the information to code for most of the functions of SV40, all of the functions of the *E. coli* galactose operon, and those functions of the lambda bacteriophage required for autonomous replication of circular DNA molecules in *E. coli*" (Jackson, Symons et al. 1972).

The experiment was not completed, however, as the introduction of the tumour virus SV40 into E.coli, which exists naturally in human and animal intestines, raised concerns about the possible consequences should the newly created organism escape from the laboratory. This incident led to a moratorium on further research and, eventually, also to the Asilomar conference, where scientists for the first time gathered in a forum to discuss the potential hazards of research (Rogers 1975). The conference ended in a provisional statement

graduating different degrees of risk inherent in different types of research. The basic categories became those of low, moderate or high containment, which eventually also found their way into official policy guidelines issued by the NIH in the USA and by the Ashby Committee in Great Britain (Wright 1994).

However, research continued on other, less hazardous organisms, and in 1974 the research group of Cohen, Boyer, Goodman, Morrow, Chang and Helling published the article "Replication and Transcription of Eukaryotic DNA in *Escherichia coli*". There, they described the successful cloning of *Xenopus laevis* DNA (a toad). For this purpose, they improved on the enzyme techniques developed by the Berg group, and they introduced the new technique of electrophoresis, by which the analysis and separation of the fragmented DNA was greatly improved.

As already described, the value of restriction enzymes consists in their ability to recognise and cut DNA at specific sequences. These sequences, called *palindromes*, share the specific that they read the same in the 5'→3' direction on both strands of DNA (Winter, Hickey et al. 2002), 265. In 1972, Vittorio Sgaramella had improved the understanding of restriction enzyme action. He had used the enzyme *Eco*RI (taken from E.coli) to obtain linear sequences of DNA from the bacterial virus P2. Following separation, he observed that the fragments would reform spontaneously, a fact that was later explained by the discovery of the so-called "sticky ends" of endonuclease-generated DNA fragments. Boyer, Goodman and Hedgpeth further elucidated this mechanism by the determination of specific sequences created by the restriction enzymes (Wright 1994). Using the same restriction enzyme for different DNAs meant that the splits in each molecule would be identical. For instance, *Eco*RI acts specifically on the sequence GAATTC, creating a cleavage between the G and the A bases:



Copied from (Winter, Hickey et al. 2002).

The results were so-called staggered (or sticky) ends, identical in both the *Xenopus* and the plasmid, which would render the two amenable for transformation, the process by which the two DNAs recombine.

The DNA of the *Xenopus* was cut with *EcoRI* and linked to the plasmid pSC101, following which it was introduced into E.coli. The new plasmid hybrid reproduced stably. The experiment was remarkable not only because of the successful cloning, but also because it deployed the new technique of (agarose gel) electrophoresis for the purification and separation of specific DNA molecules. This technique offered a simple way of analysing the fragments of DNA cut by restriction enzymes (Helling, Goodman et al. 1974). Later on, electrophoresis would prove highly valuable to the sequencing of genomes.

By this experimental result, a long standing dogma of biology was broken: the belief in the specificity of species. Although recombination occurs naturally, the crossing of species made possible by recombinant DNA technology broke with pre-existing orders, in science as well as in nature. This was in itself remarkable. But there were also other dimensions to the new technology, significantly its potential for industrial use in medicine and agriculture, and these were soon to threaten another "dogma" of science, namely its objectivity maintained through its (relative) independence from particular and private interests (Merton 1973; Krimsky 2003). A press release from Stanford University announced the *Xenopus* experiment to the larger society and the news were soon picked up by major media. The new technology, it was stated, would bring enormous benefits to society. The production of insulin, interferon and growth hormone by molecular factories was forestalled as especially promising (Wright 1994). Thus, the production of technological objects proper was starting to appear as real possibilities and not mere projections of a possible future, as was the case in the above quote from Edward Tatum's Nobel lecture.

The commercial potential of the new techniques soon became manifest on an institutional level: at the time of the press release, Stanford University applied for patents on the processes developed by Cohen, Boyer and their colleagues. This was the beginning of a new era in biology, in which high profile media coverage, venture capital investments and applied research went hand in hand. In 1981, Herbert Boyer would figure on the cover of *Time Magazine* as head of the first major biotech company, Genentech, and as biotechnology's first

multimillionaire[51]. The company, founded in 1976 by Boyer and venture capitalist Robert Swanson, was to become one of the first in a series soon counting hundreds of firms uniting pharmaceutical research and high-risk capital (Krimsky 2003).

There were also significant tendencies within the larger economy that strengthened the movement towards more commercially relevant research. As already described: Whereas state funding in the 1960s had been generous, the early 70s saw a more restrictive and selective funding policy. This tendency was further strengthened by significant macro-economical developments: In the United States, old industries like automobile, iron and textile production were challenged by competition within a globalising economy. In addition came the phenomena of "stagflation" (high inflation and high unemployment), as well as rising prices in the energy market. Hence, new and cost-effective and research-based industries were sought out, industries that would also channel money into research. Genetic engineering, along with areas such as telecommunications, semiconductors and aircraft, was singled out as one main field of investment (Wright 1994). In the years from 1975 to 1978 the number of recombinant DNA projects funded by the NIH went from 2 to 546, and investments rose from 20 thousand to 61 million dollars (*ibid*.).

That the interest of research was drawn from basic to applied science was also expressed in the choice of genes researched upon: from 'classical organisms' like mouse and *Drosophilia* to genes possessing a higher commercial and industrial potential, like hormones, interferon, insulin and vaccines (*ibid*.).

But before investments into genetic engineering could pay off, serious technical challenges remained to be solved. Research concentrated on goals central to the *control* with those pieces of DNA that was to enter into the foreign cell, the *amplification* of replication, hence efficiency, and on the *generalisation* of the techniques of genetic engineering to an increasing spectre of DNA. Most important, says Wright, was the work on gene *expression* from higher organisms in bacteria: how to get lower organisms to turn the genetic material of higher organisms into proteins useful in research and industrial production alike. The years between 1974 and 76 saw intensified research into the improvement of the newly discovered technologies:

[51] http://www.time.com/time/covers/0,16641,19810309,00.html

-new vectors were introduced (plasmids making thousands of copies in each cell; pBR322, as well as development of the lambda bacterial virus)

-new cloning techniques were taken into use. Of special significance was Temin's discovery in 1970 of the enzyme reverse transcriptase. The discovery of this enzyme, of which I will have some more to say soon, seemed to fly in the face of Crick's central dogma, as the specific action of the enzyme is to transcribe mRNA into DNA[52]. Hence it became possible to select expressed genes along a given genome for cloning. The technique was soon to be replaced by the more effective shotgun method, in which the whole genome is fragmented by the use of restriction enzymes.

-more effective methods for the selection of bacterial colonies containing specific DNA (screening of radioactively labelled DNA) were developed.

-new sequencing techniques were introduced by Sanger, Maxam and Gilbert at the Harvard University. Sequencing means the procedure by which the exact order of nucleotides along the DNA molecule is read of (Watson 1992).

Inconsistencies of biological meaning and information…

In the fall of 1977 a team lead by Boyer succeeded in synthesising the peptide hormone somatostatin and to have it expressed in *E. Coli*. From an industrial point of view, these were good news. And indeed the investments by venture capital companies as well as larger, multinational concerns sky-rocketed in the years to come, only to stagnate in 1983, as expectancies somehow cooled off (Wright 1994). At the time, major research interests were directed at the regulatory genes of higher organisms, made possible by the new recombinant and cloning techniques. But when the first results of the probes into chromosomal structure were announced, the community of researchers was in for a surprise. In accordance with the central dogma,

"It was taken for granted that the nucleotide sequences within the genes would be identical to the ones in the cDNA probes. Yet the first preliminary results indicated that the restriction fragments obtained from the segments of DNA were frequently different from the ones generated from their related cDNA probes…it seemed impossible for the cDNA (or mRNA) to be other than identical to the sequences from which they were transcribed" (Watson, Tooze et al. 1983:91).

[52] DNA transcribed in this way is known as cDNA, complementary or copy DNA.

It had been known for some time that early versions of mRNA (so-called pre-mRNAs) were cut down to shorter sequences during transcription in the nucleus. But it had been taken for granted that this processing consisted in the removal of regulatory DNA only, assumed to reside at the 5' and 3' ends of the pre-mRNA (*ibid*.). Following this logic, gene expression would still faithfully reproduce the sequence of structural genes on the DNA molecule. But now it was discovered that the DNA of higher organisms (i.e. animal viruses) was fragmented into coding (*exons*) and non-coding regions (*introns*). The introns, for which no function could be discerned, were promptly referred to as "junk DNA", and their presence raised tricky questions. In evolutionary terms: What were the introns doing there? And what remained of the strict correspondence between DNA and protein earlier found in prokaryotes? (Fox Keller 2000). The role of junk DNA still remains little understood, but the mechanism by which the introns are excised, DNA *splicing*, has been shown to consist in the joint actions of pre-mRNA and small nuclear ribonucleoproteins ("snurps"), that together make up so-called *splicosomes* (Winter, Hickey et al. 2002).

The picture was complicated further when it was discovered that splicing (or editing) would also proceed in a number of different ways, so-called *alternative splicing*. By this is meant the ways in which different mRNA transcripts are formed from the same primary transcript. The potential for variation does not end there, however: it was soon discovered that different proteins may also be synthesised from the same mRNA. Which primary transcript finally translates into which protein, then, remains a highly variable matter, depending on a range of contextual factors, among them the type of cell and its stage of development. What's further, it seems that many of these changes of the translation process also rely upon the binding of proteins to the primary transcript (the promoter site), and so in fact gene expression cannot be pictured as *initiated* by the genetic program (*qua prime mover*), at least not in higher organisms (Fox Keller 2000). There are lots of other editing mechanisms as well: DNA repair, exons from different primary transcripts are spliced ("transposable genes"), foreign bases may be introduced and so on.

In addition to the above factors, the fact should also be mentioned that a very low percentage of the genes along the chromosome actually codes for proteins ("structural genes"), maybe as little as three percent. Other kinds of genes, however, seem to exist in abundance: promoters,

terminators, activators or leaders…-genes whose roles are not connected directly to the production of proteins (*ibid*.). Also this state of affairs turned up as a result of the ability to isolate, control and sequence the expression of specific genes in vitro.

Hence, the "one gene – one enzyme" hypothesis was forever relegated to the junk-pile of history. And, speaking of higher organisms, the operon model did not fare much better. As seen, the "simple" division of operator and regulatory genes expected to be found along the DNA transcript did not appear. In stead, a variety of regulatory mechanisms turned up that pointed in the direction of contextual, not genetic, regulation of gene expression. And indeed, here we find important pointers towards dominant trends within present-day research:

> "It is from these regulatory dynamics [of the cell as a whole], and not from the gene itself, that the signal (or signals) determining the specific pattern in which the final transcript is to be formed actually comes. Unravelling the structure of such signalling pathways has become a major focus of contemporary molecular biology, and while the temptation remains strong to order these pathways as linear sequences of events deriving from the action of yet other genes, the evidence that is accumulating makes such a simple ordering ever more difficult" (*ibid*., 63).

Parts of the evidence here alluded to started accumulating already in the 1950s and 60s, but became manifest only in the late seventies with the early results of recombinant DNA technology.

However, obstacles like these did not seem to cause great concern among the gene's loudest proponents: "The focus of research was not the expression of genes in general, but the expression of genes coding for commercially important proteins" (Wright 1994:84). The first success of the new "industrial-academic complex" also came in the year of 1977, when Herbert Boyer and his team at the University of California, alongside Keiichi Itakure at the City Hope National Medical Centre in California, succeeded with the complete expression of an animal protein in bacterial culture. The final product, somatostatin, is a peptide hormone found in the brain of humans (*ibid*.).

By this time, the number of small biotech/engineering firms started to rise (Cetus, Biogen, Genex, Genentech) and an increasing number of multinational corporations were taking an interest in the field. In the beginning, this interest took the form of investments in the smaller companies. In that way the multinationals (Eli Lilly, Monsanto, Standard Oil Louisiana, Abbott Labs, Philips Petroleum, Kellogg, Dow, Hoechst, Kleiner and Perkins and so on)

could monitor the development within the field. New constellations developed between universities, governmental agencies, small engineering firms and large-scale companies. Eventually, also venture capitalist companies found their way into the business, placing high-risk investments behind the prospective developed in the engineering firms and university institutes. Later on, the large-scale companies would enter the competition in a heavier manner, establishing their own research institutes and buying expertise from the universities and engineering firms. In 1979, the Carter administration instigated a policy designed to increase cooperation between science, industry and the military which was to be continued and expanded by Reagan in the early 80s: liberalisation of patent rights, tax incentives encouraging the flow of high-risk venture capital into the new start-up companies, increased state support for research into commercially promising technologies. In England, with the election of Margaret Thatcher, similar developments took place (Wright 1986).

"From the beginning, the new firms used aggressive research and development, proprietary, and communications strategies to advance themselves" (*ibid*.). No wonder many of the prospects offered were of a rather optimistic nature, no longer guided by the research ethos of science but now also by the dynamics of venture investment and large-scale capitalism. One case in point was the joint announcement of Genentech and the City Hope National Medical Centre of the (alleged) stabilisation and expression of the gene for human insulin in E.coli. The announcement was made at a press conference, together with the announcement of a multi-million dollar contract with the pharmaceutical company Eli Lilly. However, the scientific "breakthrough" was not as original as claimed, and the results were highly premature with respect to the feasibility of the project. Says Wright:

"In summary, as genetic engineering became seen as a promising investment prospect, a turn from traditional scientific norms and practices towards a corporate standard took place. The dawn of synthetic biology coincided with the emergence of a new ethos, one radically shaped by commerce" (Wright 1994:107) [53].

[53] For an analysis of the new biotechnologies and the traditional research ethos articulated by Robert Merton, see (Krimsky 2003).

6. Re-opening the space of development: mapping and sequencing the human genome

However you consider it, the label *The Human Genome Project* is of course multiply misleading. Take it apart. "*The* human genome". As we all know, there is no one human genome…at the level of the mapping of genes the differences among individuals may be unimportant…Yet when we come to sequencing, on a scale at least a thousand times finer than gene mapping, we will be interested in precisely those stretches that we know to contain our genes and control elements and where variation is high. Here we uncover clues to disease; here may be buried our talents. Here, the preconception that there is one human genome, implicit but unexamined in the name of the project and built into the way the project is being carried out, is both false and pernicious

Horace Freeland Judson, *The Eight Day of Creation*

We have already seen how the human genome, in the 1960s and 1970s, counterfactually, came to be perceived of in terms of the genetic program, and so it is today more often than not displayed as a unified object. Referring to such different characters as Walter Gilbert, Bob Waterston and John Sulston, Adam Bostanci writes that:

"Visionary molecular biologists have always conceived of the human genome as a single natural object. Dubbing their fantastic plan of determining the sequence of its building blocks the "holy grail of genetics", they predicted that the human genome sequence would eventually become "the central organizing principle for human genetics in the next century"" (Bostanci 2004).

In what follows, I will try to reconstruct some of the developments that went into the broad establishment of the human genome as a global (in a double sense) organisational principle. The Human Genome Project emerged as the result of a complex set of scientific, technological, administrative and political factors. I will try and single out *some* of the most important of those, but it goes without saying that the complexity of the project, its contemporariness and the scope of this text do not offer the opportunity to go into details. The central point, however, is not to give a detailed historical description, but to get at the status of the genome as an action-organising principle and object. Can any conclusions be drawn as to the implications of the present state of knowledge for experimental, clinical and legal action? What kinds of clinical action does the genome permit/facilitate, and which are the significant

social implications of its implementation given the wider institutional and epistemic context to which it is shackled? When coupled to Beck's theory of first and second modernity, the case of immunology will eventually be used as a reference-point for evaluating the present situation insofar as the two objects of the antibody and the genome make up statutory cases, almost social-epistemic "ideal types", of first and second modernity.

Mapping technologies[54]

On the technical and scientific side, already mentioned developments within recombinant DNA technology were of great importance to the efforts of mapping genomes. First and foremost: restriction enzymes, allowing for sequences of DNA to be cut at specific sites, were of great importance. Together with the use of ligases these formed a basic toolbox that could be used to "cut and paste" nucleus acids. Combined with new cloning techniques (i.e. recombination in bacterial cultures through the use of vectors), these enzymes allowed for the copying of large amounts of specific gene fragments into so-called "clone libraries". Through further treatment with enzymes, new fragments of DNA ("contigs") could be made that next could be measured according to length by electrophoresis. Eventually, the resulting fragments could be pieced together so as to form a map of chromosome structure (Cook-Deegan 1994). Cloning techniques were further advanced by the ability to duplicate large chromosome sequences in yeast, so-called "Yeast Artificial Chromosomes" (YACs). These procedures, "physical mapping", allow for specific gene loci to be mapped accurately onto the chromosomes on which they reside. Later on, physical mapping has been improved, notably through different hybridisation techniques (Winter, Hickey et al. 2002), following which the ability to map genes onto their respective chromosomes have been performed with greater resolution and detail.

From a *clinical* point of view, the technique of *genetic linkage mapping*, emerging more or less simultaneously with physical mapping in the late 1970s/early 1980s, proved of more immediate value. The practical and scientific value of genetic linkage mapping lay in its ability to combine classical methods from human genetics with the new molecular genetics. Traditionally, human genetics had been cut off from the interventionist techniques of Mendelian/Morganian crossings due to physiological factors (procreation rate) and from the new molecular biology due to ethical restrictions on experiments on humans. Hence, its domain of action had been restricted to statistical correlations between family pedigrees and

[54] For a discussion of the mapping metaphor, see (Gaudilliere and Rheinberger 2004).

ordinary clinical diagnoses. However, due to increasing capabilities in mapping genes onto more or less specific chromosomal sites, it was just a question of time before genetic markers found their way into traditional mapping practices, hence establishing the first major interface between molecular genetics and clinical science. The central problem consisted in locating the genes of specific diseases along the genome when these genes themselves were unknown: At the time, the task must have seen even worse than searching for the needle in the hay-stack.

Mark Skolnick and his team of researchers at the University of Utah found a way around this problem by concentrating, not on the disease genes themselves, but on certain *markers* situated in locations nearby the genes on the same chromosome. These markers were established on the background of natural genetic variations occurring among members of the same family. If enough such variations could be found, both within single families and between different families, Skolnick and his colleagues figured out that these could be used as substitutes for the genes themselves (Cook-Deegan 1994). The rationale for this way of proceeding lay in the two following states of affairs: 1) Genetic loci occupying neighbouring or adjacent positions on the same chromosome tend to be passed on together from generation to generation. The closer the loci of two or more genes, the greater the chance of them occurring together also in the next generation, hence the greater the probability that they will *not* recombine. The distance between two or more genes can therefore be measured by *recombination frequency*, expressing the statistical probability of the two loci occurring together also in the progeny (Winter, Hickey et al. 2002). 2) The same genetic loci may be subject to a limited number of internal variances among family members. It is this state of affairs that allows for the loci to serve as markers for genetic variance: differences among the genetic markers of the individual family members are correlated to phenotype variance, i.e., the occurrence or non-occurrence of disease in the person. Hence, it becomes a question, not of finding the gene itself, but of finding markers that are sufficiently nearby the disease gene. If enough observations can be made correlating the same genetic markers with the same disease in different individuals, this will make up sufficient evidence for the genetic link to be inferred. The markers established by Skolnick and his colleagues were termed *restriction fragment length polymorphisms* (RFLPs). They were constructed by the use of specific restriction enzymes to find repeated sequences of DNA, a phenomenon occurring throughout the genome and with a frequency sufficiently high to "anchor" a map (Cook-Deegan 1994).

In the late 1970s and early 1980s then, the Utah group set out to establish enough RFLPs to map disease genes onto specific regions of different chromosomal regions. The work was supported by both the NIH and the Howard Hughes Medical Institute (a private foundation). Utah was strategically chosen because of the high numbers of Mormones in that area. Mormones keep especially close tracking of their family pedigrees due to religious reasons, and so their cooperation was another important factor for the success of the undertaking. The Utah group soon received competition from a privately funded team, that of Helen Donis-Keller from Collaborative Research, Inc. in Boston.

In spite of problems financing the undertaking (Donis-Keller was turned down first by NIH then by Wall Street) Collaborative Research continued their mapping work and the hunt for disease genes. The entry of different research teams and private capital contributed a strong sense of competitiveness to the gene hunt. With the heightened practical potential of the new molecular techniques also came a transformation of the research community:

"Despite the professional tensions, or perhaps abetted by them, the genetic linkage map beginning to coalescence around the efforts of the groups at Utah, Collaborative Research, and elsewhere became an enormously powerful tool. The number, pace and scale of hunts for human disease genes increased dramatically in the late 1980s. RFLP mapping reached a fever pitch, often flashing a sharp, competitive edge. In musing on the history of their field, geneticists James Crow and William Dove compared the 1987 'map flap' with publication of the first genetic linkage map, Alfred Sturtevant's 1913 paper on *Drosophila:* "these quiet beginnings stand in abrupt contrast to the current hubbub over the human linkage map and the proper definition of a map. With its rival factions and the glare of publicity, the mapping race is almost a genetic Olympics."Crow and Dove betray a tinge of nostalgia, even a tacit disapproval, of the style among new upstarters. But the world had changed" (Cook-Deegan 1994:71).

In the period 1983-87, several important discoveries of markers for genetic disease followed: Huntington's and Duchenne's in 1983, polycystic kidney disease, retinoblastoma and cystic fibrosis in 1985. The first genes with unknown functions were found in 1987. The greatest story of success, as described by Cook-Degan, was that of the CF marker in 1985, followed by the location of the gene itself in 1989. The consequences, although drawn on somehow optimistic premises were correctly deemed to be drastic. The New York Times pronounced that: "A new phase in the application of molecular genetics to the dissection of human inherited disease has begun". And, quoting Donis-Keller, it was announced that the new techniques "…will give choices that were never before possible" (Schmeck Jr. 1987).

DNA Sequencing

In spite of the successes of groups involved in linkage mapping, the decisive technological impetus of the Human Genome Project came from elsewhere. The techniques of linkage mapping would be helpful for locating specific genes to specific chromosomes, but they did not reveal the actual location of the disease genes (Cook-Deegan 1994). Physical mapping, on the other hand, would go some way in serving this purpose, but the problem with that technique was that it presupposed that the gene and its function was already known. The first physical maps to be made were successful largely because they were carried out on well established model organisms, like yeast and worms. These projects, then, were able to draw on bodies of knowledge that were not available to human geneticists (and would for that reason come to serve as valuable "model projects" for the Human Genome Project).

Sequencing is the systematic registration of the order of base-pairs along the DNA strand (Watson 1992). Whereas the previous mapping techniques generally presupposed that something was known about the gene and its products, i.e. that it had been expressed, sequencing meant reading off the DNA "itself", and so offered a more direct approach to mapping. In the mid 1970s, Fredrick Sanger (Cambridge) took procedures for protein and RNA sequencing (to a huge extent developed by himself) one step further and applied them to DNA. The new sequencing techniques took advantage of the naturally occurring replication process of DNA, and upon the triplet variations over the four bases A, C, G and T in each single "informational unit". Sanger found a way to mark one single base, say, G, and insert it into the replication of a single sequence. The replication process would come to a halt when reaching the position of the new, modified base, G*. For example, the sequence AGCTCCGAGGT would come out as the sequences AG* (end), AGCTCCG* (end), AGCTCCGG* (end). From this it was deduced that G was located in positions 2, 7, 9 and 10. By repeating the process with the other bases, the final sequence would in the end be established (Cook-Deegan 1994).

Sanger's accomplishment was paralleled by that of Gilbert and Maxam, who, working out of Cambridge in the USA, came up with a different sequencing method. The procedures, respectively termed the *chain termination* method (Sanger) and the *chemical degradation* method (Gilbert and Maxam) were laborious and monotonous, and were often carried out by PhD or post-doc students. In the years to come, work centred on the automation and up-speeding of the sequencing process. Most of these efforts came from companies that produced

lab equipment: “A few companies were formed to develop instruments, usually growing out of academic centres to fill market niches left vacant by larger companies” (*ibid*. 64).

Between 1983 and 1987, two teams worked hard to apply the proper technological apparatus to the automation of sequencing. Caltech[55], a public university, but supported by big companies like Monsanto and Upjohn, focused on the application of fluorescent dyeing techniques, whereas Applied Biosystems (a company) focused on detection and slab gel techniques. During a short span of time, a wide range of complementary technologies became available at the market:

> “A group from Applied Biosystems visited Caltech in the spring of 1981, just after the first gas-phase protein sequencer had been developed. Applied Biosystems later picked up the license for the protein sequencer and evinced interest in the protein synthesizer, DNA synthesis machine, DNA sequencer and other instruments under development at Caltech. With this suite of four instruments, a laboratory could break down proteins and DNA into their component sequences or build up a specified protein or DNA sequence from scratch. These were essential steps in a wide range of molecular biology experiments. Instruments to sequence and synthesise proteins and DNA formed the technological quartet for a new approach to biological research” (*ibid*., 67).

Up until that time, Beckman Instruments had been the leading company within protein synthesisers. When its founder, Beckman, who had been financing research at Caltech, learned that the protein synthesiser had been sold to a competitor, the newly founded Applied Biosystems, he became furious. But Leroy Hood, who had played a central role in both the engineering and the fund-raising process behind the new machine, felt that he was in the clear. As it was, Beckman Instruments middle manager had been offered the machine, but had turned the offer down. “Hood learned that selling a new idea required approaches to top management and also convincing middle management and corporate technical experts. Individuals at many levels could block a new idea; progress required all the gates to be open” (*ibid*.).

When the first automated DNA-sequencer eventually hit the market in 1986, it was based upon the application of fluorescent dyes to cut strands of DNA. Each of the dyes (four in number) would connect to the ends of specific pieces of DNA, depending upon which of the bases was at the end; A, C, G or T. When run through agarose gel and beamed with a laser, the different colours would identify the base by its colour. Following this, the cut pieces were re-assembled to the original sequences using computer algorithms (Indeed, the Cartesian

[55] California Institute of Technology

notion of analysis and synthesis had found its technological expression). A main difference, though, was that the sequencers and synthesizers of Applied Biosystems also allowed for the synthesis of new compounds, not previously existing in nature.

The sequencer, when completed, soon became a commercial success and spread throughout the world[56]. Being as it was itself a product of a highly competitive and commercialised cooperation between science and industry the sequencer fitted well into the global environment it now entered. Both in Europe and in Japan different sequencing efforts were well under way, usually more or less co-existent with efforts to develop own sequencing technologies. Hence, competition ranged simultaneously over the areas of science, industry and commerce, the goal being to come up with the best results, products and technologies first, thereby to gain position in the global market (Cook-Deegan 1994).

The new techniques for physical and genetic linkage mapping and DNA sequencing co-developed, and eventually came to make up complementary parts in the general process of genome mapping. Because linkage mapping served to correlate the disease gene to a specific clinical diagnosis, it was a valuable tool for anchoring (embedding) the physical map, which on its side would offer a more accurate description of the specific area on the chromosome. Sequencing, on the other hand, would be able to offer bigger maps of even higher resolution, and it would also yield structural information about so far unknown genes. Hence, in the general debate leading up to the Human Genome Project, the "trialectic" of the three technologies was often heavily underlined (Cook-Deegan 1994).

Developments within sequencing technologies and improved maps were incremental to the increasing success in finding disease genes. Whereas single gene hunts in the early 1980s had to be undertaken with no knowledge of the overall position of the relevant gene, conditions improved towards the end of that decade. Early attempts were particularly laborious: with no clue as to the position of the gene along the genome, other traces had to be followed, like knowledge of the gene product (the protein or some specific antibody connected thereto), or knowledge of the function of that gene (Strachan 1999). As mapping projects of the human genome got under way, possibilities for finding disease genes also increased. A number of different strategies and techniques had to be combined to get to the single gene: clinical,

[56] Cf. http://www.genomenewsnetwork.org/

experimental and computational. Once a candidate gene had been found, it had to be checked against mutations in affected persons. In the mid 1980s, the technique of *positional cloning*, introduced by Francis Collins, improved conditions further. The technique became possible because of improved maps, and could be used to correlate knowledge of gene positions with knowledge of mutations in affected families. The genes for Duchenne muscular dystrophy, cystic fibrosis, adult polycystic kidney disease, Huntington disease, colorectal cancer and breast cancer all were discovered using this technique (Strachan 1999).

Much of the following work went into the rationalisation of procedures, technologies and instrumentation, all in the name of faster, bigger and more accurate sequences, work that cannot be described here. One important innovation that deserves to be mentioned, however, is that of the polymerase chain reaction (PCR).

PCR is a highly efficient technique for copying DNA by way of enzyme reaction, developed by Kay Mullis at the Cetus Corporation in the mid 1980s[57]. Whereas copying sequences of DNA had been possible since the 1970s through cloning, the process was often slow and laborious. By the use of PCR, each new copy of DNA acts as a template for the synthesis of a new copy; hence the number of copies rose exponentially. Whereas cloning had been restricted to the copying of long stretches of DNA, with this new technology one was able to copy specific and also very small stretches or regions. Indeed, the bottom limit would be the single gene "itself", as long as it did not consist of less than a hundred base pairs (Doggett 1992). The process is carried out in a test tube, where template DNA is mixed with nucleotide precursors for making the new DNA and a DNA polymerase enzyme (The enzyme was called *TAQ polymerase*. 'Polymerization' denotes the process by which a number of simple molecules are formed into a compound called a polymer. A polymer*ase* acts as an enzyme in this process). The reaction is initiated by heating the mixture, whereby the two strands of DNA separate. In the original technique, this process had to be repeated for each new cycle. By 1986, the Cetus group had replaced the original enzyme with one found in hot springs, and this new enzyme made sure that DNA constantly was copied anew. Among other advantages, this allowed for the process to proceed without the need for replacing the enzyme between the cycles. Indeed, it was later asserted that "the genome project itself had become practical only in the wake of Mullis's discovery. PCR was a godsend" (*ibid*.). It should also be mentioned

[57] A close description of the process is offered in (Rabinow 1996).

that PCR has proved valuable not only to sequencing efforts, but in many other, related fields as well. Because it makes the analysis of DNA in ordinary biological samples possible, PCR is used in forensic analysis, in genetic anthropology, developmental genetics and for taking blood or tissue samples in clinical practice (Rabinow 1996).

Some policy issues

As indicated above, in the last part of the 1980s the number of obstacles to the sequencing of the human genome was great: inadequate technologies, a general lack of over-all organisation among research groups and laboratories, and correspondingly few communicative strategies to coordinate the efforts of biologists involved in different mapping projects[58]. The scientific community was generally sceptical towards any such large-scale research projects; it was clear that it would have to take a coordinated effort among groups that were not used to working in large teams (Alberts 1985). The feasibility of a sequencing project was also questioned on scientific grounds. At a meeting in Cold Spring Harbor Laboratory, put together by James Watson, the idea of a synchronised genome mapping effort was set forth. The idea stemmed from Charles Delisi of the Department of Energy (DOE), who also envisaged his department as coordinator of the project. The proposal met with massive critique from a huge number of central geneticists and molecular biologists. Strong support gathered for David Botstein, who argued that the mere size of the project would change the structure of science, and that the change might eventually turn out negative for the scientific community (Cook-Deegan 1994).

However, other forces were also in motion. The idea had been circulating, among scientists as well as administrators and policymakers. Not unimportantly, major databases resulting from DNA sequencing had already been established, one in Los Alamos, the other at the European Molecular Biology Laboratory in Heidelberg, Germany. Soon other agencies also came to concern themselves with the idea, and these were agencies that were at the very heart of policy-making and research within the life sciences. The proposal of DOE, it was argued, suffered from a general lack of biological know-how, depending too heavily on perspectives

[58] Here I refer mainly to the understanding among scientists involved in clearing up the problems involved before large-scale mapping and sequencing could take place: "The human genome project should differ from present ongoing research inasmuch as the component subprojects should have the potential to improve by 5- to 10-fold increments the scale or efficiency of mapping, sequencing, analyzing, or interpreting the information in the human genome. Progress toward all the above goals will require the establishment of well-funded central facilities, including a stock center for the cloned DNA fragments generated in the mapping and sequencing effort and a data center for the computer-based collection and distribution of large amounts of DNA sequence information" (National Research Council 1988).

from engineering, and with a too strong emphasis upon (sequencing) technology to solve the biological problems involved (not unlike the situation with the Rockefeller Foundation in the 1940s). One strong actor became the Howard Hughes Medical Institute (HHMI), in the eighties the largest private foundation supporting physiological research in the USA. In July 1986 it hosted an international meeting held at the premises of the NIH, also this fronted by central scientists like Watson and Gilbert, where the possibilities of a coordinated sequencing program was discussed anew. This time, however, the emphasis was more upon sequencing strategies as continuations of already existing mapping practices. The one without the other, it was stated, made little sense (*ibid*.). It was also a massive display of power in which the pendulum set in motion at the Cold Spring Harbor meeting (held only one month previously) seemed to have oscillated in the opposite direction:

> "The HHMI forum turned into a love fest for a redefined genome project. There were several brief presentations about the technologies and what was going on in the U.S. agencies and in other parts of the world. But mainly, it was a show of power – a battleship summit for molecular biology" (Cook-Deegan 1994:122).

One obvious reason for this change of heart was that the strongest critics from Cold Spring were not present at the HHMI meeting. However, consensus that the project should be carried out was growing, and towards the end of the 1980s the central question was not *if* there was going to be a project, but rather *how* it was to be carried out (*ibid*.).

The consensus to carry out sequencing of the human genome was strengthened by the gradual involvement of central agencies like the National Academy of Sciences and the NIH. By including well-known scientists and sceptics towards large-scale sequencing in the preparatory work, and by placing more emphasis upon linkage and physical mapping strategies, the project became more acceptable to a wider part of the scientific community, as exemplified by a conditioned approval issued by the American Society for Biochemistry and Molecular Biology in June 1987. The close connection between organisational structure and the quality of scientific work was put into clear focus. The scientific community feared a strong top-down structure in which the main premises were set by administrators and politicians, and not by scientists themselves. It should be kept in mind that, at this stage, there was no lack of mapping and sequencing data: a number of projects were already well under way, pouring data into the databases. GenBank, the database of the National Institute of General Medical Science (NIGMS), was in desperate need of upgrading in order to keep up

with developments. And so the quality of science came to be debated in terms of quality versus quantity:

"Delbecco challenged Baltimore by saying that the aggregate of cost of doing many small projects would drastically exceed the cost of an organized program. Botstein countered that the costs would be higher, but the amount of information beyond mere sequence data would also be significantly greater" (*ibid.* 140).

A closer attention to the state of the art of mapping practices seemed to clarify the matter. During work for a committee set down by the NAS to clear technical and scientific issues involved in the project, Maynard Olson's reference to the tradition instigated by Fredrick Sanger in Cambridge, England, won strong support. Sanger's strategy was to aim for the limits of the technically feasible so as to integrate technological developments into the mapping project as it was progressing, a gradual up-scaling (*ibid*.).

It should also be noted how the involvement of the NIH meant closer connections to both scientists and politicians due to the special position of that organisation. It already occupied a central mediating position between the two groups, being as it was (is) the largest research funding agency for the biomedical sciences in the U.S and enjoying great popularity in Congress. At the same time it was (is) not tied down by the restrictions normally applying to administrative agencies or departments (i.e. it posited wide discretionary powers). Director James Wyngarden did an important job by introducing the project in political circles and by rendering it compatible with the complex appropriations process necessary to secure support from Congress (*ibid*.). As described by Cook-Deegan, this operation of translating scientific goals and needs into an administrative and politically comprehensive language was instrumental in the establishment of political support for the project.

Some developments on the ground…

During the 1980s a large number of private as well as public mapping centres and research groups came into being. By 1987 it was estimated that a number of 4 257 human genes were identified. About 1 200 of these had been mapped onto specific chromosomes or chromosomal regions (Office of Technology Assessment 1988). At the time, the total number of genes was estimated to somewhere between 80 and 100 000; in more recent times these numbers have been corrected to somewhere between 20 and 25 000 (Coghlan 2004). In addition, the mapping of the genomes of several other organisms was also well under way. These other genome projects were deemed highly valuable also for the sake of mapping the

human genome, -as well-studied model organisms they served important clues to the correlation of gene and gene product also in humans.

Percentage of genome sequenced in some well-studied organisms in 1988

Organism	Genome size (base pairs)	% sequenced
Escherichia coli bacterium)	4.7 million	16
*Saccaromyces cerevisiae (*yeast)	15 million	4
Caenorhebditis elegans (nematode)	80 million	.06
Drosophila melanogaster (fruit fly)	155 million	.26
Mus musculs (mouse)	3 billion	.04
Homo sapiens (human)	2.8 billion	.08

Source: (Office of Technology Assessment 1988).

Concomitant with technological developments and the liberalised economic policies of the Reagan-era, a highly competitive environment emerged in which human disease genes occupied a privileged position. The main target was the classic Mendelian disorders, of which there are not many, and so the stakes were high. For those who succeeded, the award would be funding, prestige and patentability rights (Hilgartner 2004).

Two different approaches came to define mapping and sequencing practices (*ibid*.). One, typically connected to smaller, private enterprises, was that of "gene hunting", in which the focus was upon the identification and isolation of Mendelian disease genes. The other, more identified with larger, often publicly funded laboratories, was seeking to map the overall structure of whole genomes or chromosomes. For this latter purpose, low-resolution mapping techniques were of primary importance, whereas gene hunting, concentrating on much smaller regions, would aim for high-resolution maps. Now, it can easily be imagined that these two practices did not exist in total separation, but were involved in a complex dialectic in which the exchange of information played an essential role. Clones or maps from one mapping laboratory could be used by gene hunters and vice versa. What was more, the laboratory equipment deployed were the same in both lab types, and scientists would frequently work in projects of both kinds (*ibid*.).

Mapping and sequencing ideologies

The issue of *patentability* proved a particularly hard case when it came to the sequencing of the human genome. So far, patentability had been restricted to the procedures of mapping techniques and markers, like the RFLPs, and their products, isolated genes. With respect to patentability, single genes that had been isolated and purified did not constitute any significant legal differences from the patents that emerged with the coming of recombinant DNA technology.

Also in the mapping field ideological differences reigned within the mapping communities: the Hughes Institute at the Utah University and Collaborative Research each possessed about 600 markers. Whereas the Utah Group would go public instantly after a new discovery, Collaborative would not. Because markers are in-exact, giving away information to a competing company could result in that company coming up with an even more exact marker, which would then out-do the scientific relevance of the first, more imprecise marker. Hence, keeping quiet gave a competitive edge (Roberts 1987).

But when it came to *sequence data* the issue proved even harder to settle. In 1987, Walter Gilbert provoked the whole scientific community when he resigned from a public committee on the genome project established by the NRC, and announced his intention to carry out the sequencing of the genome in a private company, the Genome Corporation (Cook-Deegan 1994). As sequencing would not yield indirect access to genes, but rather direct access to the "genes themselves", i.e. to the exact base sequences, the question arose as to whom the genome actually belonged (Roberts 1987). Two poles emerged, one "public" and one "private", the first claiming the genome to be the collective property of the human race, the other denying the validity of the basic premises of the argument. Typically, as argued by Gilbert: "the sequence data is not identical with the genome itself; hence the *data* can be patented" (*ibid*.). Obviously the question was of huge significance for those with industrial and commercial interests in the new technologies: "A key question for industry…is how to protect our investment and collaborate with scientists. We need new mechanisms to protect our rights or it will not work…For 90 % of the work we do, we don't see how we can share it", Bernadette Alford, Collaborative Lawyer, quoted in (*ibid*.). Two problems emerged: First, whereas mapping and sequencing data were highly scarce resources to be protected, there was also a need to share work. Hence, data exchange was often entangled in complex strategies of give-and-take among the actors involved (especially among the disease hunters), in many

cases leading to relations of mutual distrust (Hilgartner 2004). Second, in the question of patentability, case law was restricted to *tangible* property, whereas sequence data is immaterial. No precedent existed for the legal battles that would follow (Eisenberg 2002). The patenting debate would follow and structure the Human Genome Project in important ways in the years to come. I return to this problem in the chapter on patentability.

For most practical purposes then, the ideal types of "public" or "private" were already muddled up (Gieryn 1998), hurdled into the dynamics of second modernity where long accustomed categories lose their sense and re-emerge within new conceptual contexts and institutional configurations (Beck and Bonss 2001). As stated in one *Science* article, "…the majority of the nation's leading molecular biologists have corporate ties of some kind" (Roberts 1987). Hence, in the United States at least, most molecular biologists working for public or other non-commercial organisations were also, in some way or other, working for private companies, so that, beyond the purely conceptual level, it became notoriously difficult to differentiate the one from the other.

Integrating policies

But strong incentives were also pulling in the direction of a more sharing, coordinated effort: given the state of available technology, the shear size of the task was enormous, not to say insurmountable. Hence, the necessity of sharing tasks and exchanging information about the different parts of the genome was strong. Given the coexistence of needs for cooperation and the obstacles to such cooperation posed by the strong competitiveness of the field, it may not surprise that a more coordinated effort emerged as the best option. In 1988, two central policy documents emerged in the United States, one made by the Office of Technology Assessment[59] (OTA), the other by the National Research Council (NRC). By the first, it was noted that:

"…some general ethical questions are moot because of contemporary realities, for example, the question of whether there should be any human genome mapping and sequencing activities at all. The question is moot because mapping and sequencing projects have been underway for over a decade and there has been no concerted effort to prohibit them. The more immediate questions, therefore, are how these projects should best proceed from now on and what use should be made of new genetic information" (Office of Technology Assessment 1988).

The conclusion seemed inevitable. The National Research Council saw things the same way:

"…it should be noted that RFLPs will continue to be developed, maps will be made, and genetic counselling will occur even without a concerted effort to map and sequence the human genome. The

[59] The group behind this report had Robert Cook-Deegan as its project director.

greater coordination and quality control that will result from a concerted effort will in fact benefit the public by reducing the chance of misuse of poorly organized information" (National Research Council 1988).

It is likely that reasons like these counted strongly for many initial critics that eventually came out as proponents of a concerted genome effort. Still, at this stage there was no direct suggestion of a single project. Referring to *a* human genome project, DOE wrote that

"the term is a useful way to link research initiatives and to distinguish them from ongoing programs for budget planning. It highlights the *ultimate* objective- understanding human biology by developing a new set of research resources – and captures political support and broad public interest. It has had the effect, however, of generating rancorous debate which has inhibited the development of consensus on how to improve the research infrastructure. The importance of maps, databases, and repositories has been obscured by the controversy over massive DNA sequencing" (Office of Technology Assessment 1988).

Concerted mapping and sequencing efforts, then, were displayed as natural continuations of existing mapping practices, and as "bottom-up" rather than "top-down". This integrative attitude also seemed to characterise the general epistemic status of genomic data: the exclusive status often ascribed to genetics was to be integrated within the larger field of biology:

"The Human Genome Project invites confusion by implying that the human genome will be understood when the project is over. The immediate goal of genome projects is not complete understanding, but creating tools to bring about such understanding in the 21st century. Understanding encompasses all biomedical research; it does not distinguish genome projects from others" (*ibid*.).

In retrospect, this humble approach is understandable due to the high levels of conflict generated by rumours of a monolithic sequencing project, and by the need to get on with more practical issues. Still, it would only last two years before *The* Genome Project was actually up and running. And, in spite of the integrative approach taken in the report, the gene-centrism of the central dogma was never really questioned: "The information in a genome is the fundamental description of a living system—it is what the cell uses to construct a copy of itself—and so is of fundamental concern to biologists" (*ibid*.). Indeed, the study was introduced by the bold conjecture that "the mysteries of inheritance are surrendering to modern biology" (*ibid*.).

The listing of diagnostics for single gene disorders was impressive, among the most central examples were Duchenne muscular dystrophy, Cystic fibrosis, Huntington's, Sickle cell

anemia, Hemophilia, Beta-Thalassemia, Chronic granulomatous disease, Phenylkotonuria, Polycystic kidney disease and Retinoblastina (*ibid*.). Diagnostic tests for these diseases were already developed or being developed by companies such as Cetus and Collaborative Research. The list of polygenic disorders, like cancer, coronary heart disease and diabetes, which according to the premises laid out in the OTA-report (OTA 1988) make up the overwhelming majority of diseases, did not parallel this progress. The report confined itself to noticing the positive prospects for diagnosing also these diseases (the ultimate goal, although not explicitly stated, being that of prediction). The section on *therapies* was not much longer. To an even stronger degree, here the rewards were presented as future rather than present. Then, as today, a key problem was that of protein folding, calling for a wide approach: "Advances in the development of human therapeutic products will be made more rapidly if research in the areas of protein engineering, the relationship of protein structure to function, rational drug design, and others parallels genome mapping efforts" (*ibid*.).

Although the report noted the tendency of a growing divide between diagnostic and therapeutic ability, the "therapeutic gap" was not made a problem as such. The report from the National Research Council, however, remarked that

> "Where there is no effective therapy, new abilities to detect diseases in advance of their onset create harder choices for clinicians and patients. As we explore the human genome, more people will be faced with the dilemma that now faces those at risk for Huntington's disease: Is it better or not to know one's fate when it is out of one's control?" (NRC 1988)

But also in this version there was no way around the dilemma, as the problem was so intimately entwined with the cure:

> "At the same time, the very discoveries that exacerbate those dilemmas will also be crucial steps in developing of new therapies that can help resolve them. It will be important as the project proceeds to pursue those steps and attempt to narrow, rather than widen, the gap between our abilities to diagnose and treat disease" (National Research Council 1988).

Two goals stood out in the work to come: the development of new technologies and methodologies, and the development of a new infrastructure specifically suited for genetics. The work was (somehow) to be shared between the four main agencies already involved, the National Institutes of Health, Department of Energy, the National Science Foundation and the Howard Hughes Medical Institute (Office of Technology Assessment 1988). But as to who

was finally going to head the project dissent continued in the agencies, in Congress and among scientists, the two relevant options being NIH and DOE.

The Human Genome Project

The prospects of a coordinated, large-scale genome project also met with fierce opposition inside the NIH itself. Ruth Kirchstein, director of the institute presiding over the genome program (NIGMS), wanted to protect basic science from undue political influence. Her way of achieving this was to keep things running as usual, genome research being carried out in smaller, relatively independent units (hence, she remained in accordance with many of the critics of the genome project). James Watson and NIH director James Wyngarden were directly opposed to this policy: if the NIH was to occupy a central position in the genome efforts, it would have to seize the moment so as not to lose the initiative to DOE. The NIH was by many seen as the legitimate agency for the task, but compared to DOE it had moved slowly, and so ran the risk of losing out. As described by Cook-Deegan, Wyngarden secured the leading position of the NIH by a few masterstrokes: he got the budget accepted by Congress, he established a bureaucratic centre for genome research and he appointed Watson its director. In October 1988, Watson became associate director of the NIH and head of the newly established Office of Human Genome Research, which was later to become the National Center for Human Genome Research (Cook-Deegan 1994). Watson did not proceed with great discretion:

> "Watson's scientific and administrative careers were built on an independent sense of priorities. "Just do good, and don't care if it doesn't seem good to others". His highly intuitive manner focused on character judgments and results, and scientific results were the ones that counted most. Good science was elevated to a guiding moral principle" (*ibid*. 168).

But even this characteristic did not stick absolutely: One of Watson's first moves, to the astonishment of many, was to reserve a certain amount of the NIH genome budget for research upon ethical, social and legal dimensions of genetics.

The official beginning of the genome project in October 1990 was preceded by a long and heated debate over the allocation of research funds. Critics claimed that the project would occupy an untoward part of the general NIH budget for biomedical sciences, and that it would be at the expense of smaller, researcher-initiated projects. Proponents downplayed the size of the project and focused on the (alleged) positive effects of a concerted effort. A survey conducted at the UCLA found that, whereas support for the genome project was strong in

government and (the pharmaceutical) industry, among academic scientists the number of proponents and opponents more or less cancelled each other out (*ibid*.).

Integrating strategies

Two strategies came to be decisive to the practical goals of improving technology and communications among researchers. Both were central parts of the emerging 5-year plan established by NIH and DOE at the outset of the genome project. These were: 1) the development of so-called STSs, "sequence-tagged sites", and 2) the up-scaling of certain research facilities to so-called "genome centres" (Hilgartner 1995; Hilgartner 2004).

Sequence tagged sites were introduced by Olson, Hood, Cantor and Botstein during work for an advisory group set down by Congress. The mandate of the group was to give scientific advice for the already mentioned 5-year plan. An STS is a unique sequence along the genome (Doggett 1992). Due to its uniqueness it serves well as a marker, or a "landmark" of a gene (Doggett 1992; Hilgartner 1995). As argued by its creators, the STS had many advantages over ordinary markers used in existing physical or genetic maps. First of all, it dispersed genomic information among users. It was not based upon physical access to cloned gene segments, as kept in the libraries of the biggest laboratories, but upon the more recent PCR technology. Using PCR, a spectre of polymerases of differing substrate specificity was obtained. These, in turn, would serve to define given markers along the genome. Hence, the specificity of the gene sequence (the marker) was defined by its reaction to an enzyme (PCR), and not by some previously identified and cloned segment existing in a DNA library. This meant that researchers all over the world would be able to localise markers by using the right PCR (which was commercially available). Hence, the vital information could be stored in a databank accessible to everybody within the research community. Second, it could be used as a "common language" for uniting previously incommensurable markers established through different mapping techniques, such as for instance restriction maps or contig maps (Hilgartner 1995). It would also be capable of synthesising information from genetic linkage maps with that from different physical maps, and these maps could also be synthesised with sequence data. The objective was to translate all existing maps into STS marker maps and to store the resulting information in common databases, thus uniting the efforts of previously unrelated mapping communities. As described by Hilgartner (2004) this would also serve as a powerful management tool, as a technology for holding genome centres accountable to a centralised administrative agency (NIH) and to Congress. The productivity of a certain group could be

measured in numbers of STSs established by that group, and the quality of a map could be measured according to number of STS along a certain region. In the end, it could also serve as a means for holding the genome project as such accountable to politicians (Hilgartner 1995).

Concerning the establishment of *genome centres*, this was a direct response to the need for more large-scale research units, as opposed to the smaller, traditional laboratories of biology. This also entailed a change of working style: from experimentalist, "bench-style" approach carried out by individuals or small teams, to one of interdisciplinary, cost-intensive work centred round a common goal of high throughput data accumulation. The amount of automation and repetition involved in mapping and sequencing was grist to the mill for those who argued that the quality of science would decay in inverse proportion to the amount of data produced. Many other concerns were repeated as well, for instance that the centres would take funding from smaller facilities and that they would gain too exclusive access to information (Hilgartner 2004).

Due to the critically exposed position of the project, NIH and DOE decided upon a stricter policy of planning than usual in NIH-funded projects. As opposed to a traditional attitude of "laissez-faire" as soon as money was granted a project, a more integrative approach of science and administration was sought out. There was a need to keep the project on track with respect to achieving its central goals and not invoke further criticism. For this sake, the use of STSs became a central administrative as well as a technical tool (relating to Rheinberger's terminology we thus see that administration made its way well into the laboratory through gaining control with technical things). It became possible to set quantifiable goals for mapping and sequencing, and it became possible to monitor the advancement towards that goal by requiring progress reports (*ibid*.).

By the end of the five-year period, much of the criticism directed at the project from the scientific community had diminished. Important reasons were that it had grown to encompass more and broader concerns than first assumed by many, among them the mapping and sequencing of a number of other organisms as well. Indeed, this was also a scientifically good strategy because of the need for model projects after which to shape the sequencing of the human genome in the years to follow (Cook-Deegan 1994). But it was also a result of the fact that the project did indeed achieve its goals within the scheduled time, and, importantly, that it

produced and distributed new data generously among other users. Hilgartner, in summing up the first five years of the HGP, writes that

"strategies for governing genome centers were built into the policies of funding agencies, the material forms of laboratories, the social relations among laboratories, and even the maps themselves. Through such strategies, the HGP succeeded in constituting American genome centers as accountable entities, allowing the proponents of the project to assure the scientific community that these centers would give back more than they would take. But creating centers that simultaneously solved the prevailing problems of technical and social order in the American context by no means produced stability in the rapidly moving world of genomics. To be sure, finding solutions to these problems helped justify a continuing infusion of government funds and scientific talent. But the production of better genome maps and the expansion of genome databases in the first years of the 1990s generated unprecedented commercial interest in the field, contributing to the rise of "private" genomics and, in turn, raising new problems of technological and social order" (Hilgartner 2004).

Although it may be said that the HGP simply channelled and organised developments that were already taking place, there can be little doubt that the restructurings of its first years strengthened the notion of the genome as the fundamental unit of physiological and pathological explanation:

"The penultimate level of the maps is the developmental: what we want is the map to show us what gets turned on and off in temporal order during the human creature's lifetime, to answer the intractable questions of embryology, of differentiation. Special versions of the map will be clinical, dealing, say, with inborn errors of metabolism and their cure by gene therapy, or with the cancers and their prevention (Freeland Judson 1992).

As described, this required a number of organisational, technological, scientific and administrative rearrangements. During these processes, the genome emerged as much more than a research-guiding principle restricted to the laboratories. But this was only the beginning of a number of "revolutions" that were already taking place and would continue to take place. A massive integration of disciplines were required for a complete understanding of the genome: "…protein chemistry, mass spectrometry, nucleic acids chemistry, large-scale DNA sequencing, genetic mapping, DNA diagnostics, and computational techniques" (Hood 1992). In some of its most ardent proponents, of whom Leroy Hood was a good example, there were no limits to the potential of the genome as an organising principle:

"Once the 100,000 human genes have been identified, they will be used as therapeutic reagents for dealing with all aspects of human disease…New industrial opportunities will arise from DNA diagnostics…There will be striking future industrial opportunities in biocomputing…In the future, there may be more than one hundred distinct biological databases…It will be an enormous challenge to maintain these data bases as well as to make all of them readily accessible to the biologist or physician user. The development of new object-oriented data bases, which can organize information in

keeping with its functional attributes, provide interesting new possibilities for instantaneous accessibility" (*ibid*).

Finally, technology would provide the solutions to age-old problems of biology: "Neither developmental biology nor protein folding is a problem inherent to the genome project; rather, the genome project will provide new tools for attacking these problems in other areas of biology" (*ibid*).

Although sometimes extreme in its technological optimism, there is no mistaking the general tendency: a reconfiguration of experimental and pathological space through the loophole of powerful information technology designed to relate the most distant sites on the genome with the widespread community of researchers, and make of them a functional whole. A corresponding education of medical doctors, especially in new drug-related therapies, would have to follow in order for technology transfer to be successful. This would also have to be accompanied by a corresponding "education" of the population in matters genetic:

"Scientific expertise among specialists must be accompanied by public understanding or problems will surely arise. If DNA analysis is to be more widely used in the future, then the general population must be provided with a basic genetic understanding – not that everybody should become a molecular biologist, but people should comprehend the implications of the information that becomes available. In particular, the issue of genetic carrier status must be fully explained. Some of these educational issues include the significance of carrier status to personal health, job selection, insurability, and informed options for childbearing. Moreover, the importance of improving science education, from kindergarten through twelfth grade, cannot be overemphasized" (Caskey 1992).

Statements like these abound in policy-documents and popularisations surrounding the HGP, and they betray a lot about the views about human agency, social forces and the preconditions of social action entailed by many of the project's protagonists. Technology transfer, from the scientific context to the clinical and public domains, is depicted in a linear manner, as direct application of the techno-medical object facilitated and accompanied by the proper information, the main parameters for assessment being those of cost-benefit, risk-ratio (risk vs. potential benefit) and utility. The "users", first and foremost patients, but also medical doctors, are presupposed as rational agents planning their actions in correspondence with the alternatives handed to them by the basic sciences, not unlike Claude Bernard's vision of experimental medicine from 1865 (Bernard 1957). As will be seen later on, linear representations of technology and technology transfer were strengthened by a strong turn in research policy during the 1980s, one which radically came to underline the commercial aspects of genetics and genomics, and which tended towards aligning social value of medical

technologies with commercial viability. This vision was being strongly promoted through a liberal and expanding patent policy (Office of Technology Assessment 1988; Kevles 1998; Krimsky 2003).

Two genome centres emerged as "model organisations" for future sequencing of the human genome: the Sanger Centre in Cambridge, England, and The Institute of Genomic Research (TIGR) in Maryland. Granted that the genome is embedded *qua* organisational principle in complex networks of institutional, computational, instrumental and experimental practices, it should not come as a surprise that difference of organisational structure will also yield different epistemic commitments, perhaps also different genomes (Bostanci 2004). This is indeed what happened as these two centres came to develop two different maps and two different versions of what the genome was supposed to be. The two versions would be projected through the structures of the Human Genome Project on one hand, and through Celera Genomics on the other, both presenting their maps at the same time in 2001, four years ahead of the scheduled termini of the Human Genome Project.

TIGR

Craig Venter set up the TIGR institute following his resignation from an NIH laboratory in 1992. He had left following a bitter-felt controversy over patenting rights with James Watson, and due to lack of funding for a proposed project to sequence protein-coding DNA ("ESTs") from human brain tissue. The case will be described in some more detail in the chapter on patentability.

The scientific strategy proposed by Venter diverted from the established practice of sequencing single genes one at a time. Normal practice would be to isolate and then sequence a specific gene of known function, based on knowledge derived from genetic or physical maps. To Venter, this strategy was too slow and laborious: as only a small percentage of the genome actually codes for protein, normal mapping procedure would have to work itself through a whole lot of "junk DNA" before getting to the interesting parts, the coding regions. A normal gene-hunt would start out by an approximate knowledge of the region of a gene of known function, and then work itself through that region until the sought-after gene had been localised. As described earlier, the way to isolate single genes during the early years of recombinant DNA technology, had been to isolate messenger RNA coding for a specific protein, then to convert the RNA back into DNA using reverse transcriptase. In that way, a

whole repository of cloned DNA, possibly comprising thousands of genes of unknown function, would be established before the actual gene was hit upon (Davies 2001:57-59).

Venter's idea was to take advantage of the DNA libraries thus established during ordinary gene hunts and to run them through large-scale sequencing machines. Although he would not know the function of the sequenced genes, he would at least know that they coded for some protein, and hence would be more likely to be of interest, both scientifically and commercially. For his first project, he focused upon cDNA libraries established from cDNAs from the human brain, as this is an organ particularly rich in protein-coding genes:

> "Together with Mark Adams, a research associate in his lab, Venter chose a brain cDNA library containing potentially tens of thousands of genes that are active in the brain. It was a routine process to pick a few dozen bacterial colonies, each containing the cDNA of a mystery gene expressed in the brain, purify the DNA, perform the sequencing reactions, and determine the sequence on the ABI machine. Finally, Venter would compare the DNA sequence of the two hundred to three hundred bases that he typically obtained from each cDNA with previously identified genes from a variety of species whose sequences were already in the public gene database" (*ibid*.,57-58).

Venter was a pioneer in the heavy application of sequencers to genomics research. When his application was turned down, it was both because a general scepticism towards mapping by sequencing still prevailed, and because of his announced intent to patent the sequences. The event sparked a general debate which also ended with the resignation of Watson, who did not approve of the generally positive stance eventually taken towards sequencing and patentability in the NIH (Cook-Deegan 1994; Shreeve 2004). Instead of using public money, TIGR was funded by the New York company HealthCare Investment Corporation. In return for the funding, the company was to get the property rights for any commercially viable products the institute would come up with (Shreeve 2004).

One of Watson's reasons for opposing Venter's proposal was related to already described differences in mapping and sequencing strategies. Although recognising the rationale in going for the protein-producing genes only, Watson had committed himself to the gradual up-scaling of the sequencing project, meaning that it would start with already mapped regions so as to establish a complete map and never to get too far off the ground with the sequencing work. The sequences produced at TIGR were of unknown genetic origin and would have to be mapped after sequencing in stead of before. Hence, one criticism directed at Venter was that he would do the easy work of sequencing the interesting parts of the genome, while relying

upon others to perform the less attractive job of establishing the function of that gene within the larger context of the genome as a whole. What was the role of regulatory genes in the expression of the gene in question? By focusing exclusively upon protein-coding DNA this question was overlooked. Hence, the determination of the role of the huge amounts of "junk DNA" would also be left to others (Sulston and Ferry 2002). Furthermore, as the above quote indicates, Venter's procedure was also dependent upon the public databases in order to establish the function of the sequenced genes. Insofar, then, as Venter's approach came to be established as a competitive alternative to ordinary mapping and sequencing, not as complementary, it represented a threat to the established working methods of the scientific community. Says John Sulston, leader of the sequencing centre in Cambridge: "I was in no doubt that in the long run sequencing the complete genome would be the only way to find all the genes. I saw Craig's challenge as a threat to what we were doing" (*ibid*., 125).

The general approach introduced at TIGR, and later by Celera, is that of *whole-genome shotgun* sequencing. Due to limitations in computational powers, the genome cannot be sequenced in one operation but must be sequenced piece by piece. Genomic DNA is therefore cut into pieces, inserted into plasmids and then sequenced separately. Because the resulting sequences will be overlapping, a computer program can work out their internal relations and piece them back together. According to critics of the whole-genome shotgun method, it is unreliable because of the large segments of sequences put into one single operation. This increases the chances for mutated versions of some sequence to drift to other parts of the genome, causing the sequence to be mapped onto the wrong region (misassembly). This source of error is drastically reduced by the use of the *hierarchical* shotgun-method, which was the one championed at the Sanger Centre (Bostanci 2004).

The Sanger Centre

Although work at the Sanger centre was also funded by private capital, it was not by venture investors but rather by a charitable organisation, the Wellcome Trust. The work was a continuation of the previous mapping of the genome of the worm *C. elegans,* carried out by John Sulston in Cambridge and Alan Coulson and Bob Waterston at the Washington University. Because they already had the (worm) map, there was no need to sequence the whole genome in one operation: one could sequence parts whose position along the genome was already known by marker sequences taken from the physical map. In short, the genome was split into several thousand regions which were then inserted into so-called BACs,

bacterial artificial chromosomes. Following this, the BACs were matched with the markers and finally assembled (*ibid.*)

Thus, by dividing work into parts corresponding to their position on the physical map, chances of error were greatly reduced. In this way, the map not only served to organise the finished sequence, it also served to share tasks within laboratories and between different laboratories, significantly between Cambridge and St. Louis, where Waterston had settled (*ibid*.). *C. elegans* had been chosen as a model organism for the understanding of cellular development and differentiation by Sydney Brenner in the late 1960s (Cook-Deegan 1994). Because the worm had already been studied for many years, the sequencing efforts came to be seen much more as a communal effort enjoying wide support both in the worm mapping community and in the genetics community more generally: "I feel it has been not so much a map as a means of communication", J. Sulston quoted from (Bostanci 2004). The results were published in a common data-base accessible to all.

The downside of the hierarchical model is that it is time- and cost demanding, and so friction was likely to rise with the ever-increasing demands on higher throughput at the genome centres (Hilgartner 2004). Hence, the project drew some criticism for its cost-efficiency as well as for producing allegedly unnecessary information, i.e. the sequencing of non-coding parts on the genome. But by thus remaining embedded within the research community and in the mapping tradition the centre retained a high level of trust as well as legitimacy by keeping the focus steady on the production of low-risk information. At the Human Genome Summit in 1994, the Sanger Centre emerged as a model for the future organisation and collaboration among genome centres around the world (Bostanci 2004).

Whereas the mapping of *C. elegans* could proceed according to an already established physical map, the same was not the case with the human genome. Based upon earlier genetic and physical markers, a unified digital map was elaborated, and each genome centre then had to establish a repository of DNA sequences corresponding to the part of the genome that it was working on. Parts of the genome were allocated according to its own "sequencing etiquette", the entitlement of a region being assigned according to previous sequencing work (*ibid*.). The parts were distributed to the different centres during an international conference held at Bermuda in 1996. During that meeting, some general rules concerning patenting and data release were also agreed upon:

- sequence assemblies larger than 1 kb were to be released as soon as possible, preferably within 24 hours
- annotated sequences are to be immediately published
- the entire sequence of the human genome is to made freely available to research and development in order to maximise the benefits to society (Sulston 2002).

After the initial five years, a draft phase followed, in which most of the information for the project was gathered by genome centres around the world (Collins 2004). In spite of differences TIGR had continued to work within the fold of the Human Genome Project. Eight centres emerged as leading: that of the Sanger Centre in Cambridge, England (John Sulston) was responsible for 30 % of the sequencing; six NIH funded centres should carry out 60 % , among them those of Bob Waterston in St. Louis and Eric Lander at the MIT-Whitehead Institute, and a DOE-funded centre, Joint Genome Institute would do the 10% rest (http://doegenomes.org/).

In 1997 arguments were raised that the concerted effort ought to proceed by whole-genome shotgun sequencing in stead of the Sanger model (Weber and Myers 1997). This sparked a debate in which also the general status of the genome itself was questioned (Bostanci 2004). The main thrust of the argument, put forward by Jim Weber and Gene Myers, was that the whole-genome approach would attain the goals of the HGP faster and cheaper and even at a better quality. It was argued that the whole-genome would produce more polymorphisms, the central marker of genetic variation. The proposal also rose out of a feeling that the HGP was moving too slowly: “We should generate as much of the critical sequence information as rapidly as possible and leave cleanup of gaps and problematic regions for future years” (Weber and Myers 1997). The use of existing maps for organising the concerted effort, was held against the HGP, as the division of the map into parts would lead to an “artificial coverage of the genome” (Weber and Myers 1997).

The successful sequencing of three bacterial genomes at TIGR was used to back up the argument. However, as the method was only being used actively at TIGR, taking the proposal seriously would mean a rather large re-organisation of the whole project. According to the whole-genome shotgun model, sequencing would be distributed among genome centres

throughout the world, but the finishing stage, assembling the sequence data, would have to take place in one central facility in stead of being carried out in the different centres.

The proposal met with stark critique from Phil Green, who argued that the method of computer simulation deployed by Weber and Meyer was a rather poor substitute for the already existing map that served as the basis for the HGP. Although at this stage only a few percents of the genome had been sequenced, it would also be a bad choice to change strategy now that the project was well under way. Green further argued that the whole-genome approach was unreliable and would result in a map of lower quality, significantly because of the indiscriminate treatment of the whole genome method in which problematic regions were treated on a par with non-coding regions. The danger of misassembly would also be far greater, and errors were not likely to be discovered until years later due to the massive amount of data generated at once.

Arguments like these indicated deeper differences in opinions about what the map was supposed to be. For Green, the main purpose was the gradual establishing of a complete map of the genome, which eventually could serve as a "gold standard" reference for assessing human (genetic) differences. Myer and Weber's suggestion to have a go at the whole genome in one step entailed a "monolithic approach incompatible with clone-by-clone sequencing" (Green 1997). The spatial divisions of the genome in the two different maps corresponded to the division of work in the two models: in one, work was shared and planned according to a prior topology, in the other the topology would emerge during assembly in one large centre (Bostanci 2004).

But the main significance of the debate was yet to be seen: in 1998, Craig Venter left the Human Genome Project to form the private company Celera. Together with Tom Hunkapillar of Applied Biosystems, main producer of automated sequencers, he set out to sequence the genome on private hands by using the whole-genome shotgun method. Hand in hand with the announcement of the alternative genome project, Venter declared that he would patent a number of 100 to 300 of the sequenced genes. However, the number was not important: Venter also claimed that he could carry out the sequencing much faster than the HGP. If this projection came through, he would still be in the position of patenting thousands of genes before the HGP had finished (Davies 2001). As could be expected, the initiative caused massive criticism, both from scientific peers and from the wider public. With respect to the

scientific community, this was quite understandable: "We are changing the rules and that upsets people", Venter quoted from (Bostanci 2004). By breaking with the sequencing etiquette and with the Bermuda principles, Venter also broke with the public commitments made by the leaders of the HGP, thus also with the accepted projection of what the genome was going to be. Celera's project was described by its critics as a "land grab", in which the ground of the public effort was torn away even before it had been established (*ibid.*).

People like Watson and Sulston were determined to establish the genome as a public and freely available repository of information. As argued by Sulston, it belonged to humanity's common heritage, not to some private investment firm. This meant that whereas the genome could serve as a starting point for developing patentable products, the sequence itself could not be the object of patenting:

"The principles of accessibility and on-the-spot release mean that anyone in the international biological community can use the data and ultimately turn them into new inventions that are eligible for patents. But when the raw sequence is released publicly, it will be unpatentable. It promised well that so many people came to share a vision of the genome sequence as the heritage of humanity, as stated in Article 1 of the universal declaration on the human genome and human rights, which emerged from Unesco's general conference in 1997" (Sulston 2002).

But in important ways, it was already too late: As described, the NIH itself had been drawn into the patenting game in 1991, when Venter first proposed the patenting of specific sequences. The proposal was supported, to Watson's great dismay, by director Bernadine Healey, who mainly proceeded on a precautionary rationale: if the NIH did not move to secure property rights fast, someone else would surely do. Hence, it was also a matter of securing the position of American prominence in research and industry:

"My God, if this thing doesn't get done in a substantive way in the United States, that is the end of biotechnology in the U.S…There is a tremendous effort in France, England, and Japan…If this becomes a race and if gene fragments become proprietary, then it is in the best interest of the U.S. and entities of the U.S. to file for patents", Wallace Steinberg of the HealthCare Investment Corp, quoted in (Cook-Deegan 1994).

Due to great uncertainty as to the role of patentability and genomics in the future, it was best to play safe. *Seemingly* ironically, it could also be argued that the best way to secure the public accessability was for public institutions to seek for intellectual property rights. Indeed, this had been the practice in many universities and research facilities since the dawn of the 1980s. The irony was not complete, however, as the patenting institute had always been meant

as an incitement to promote innovation and development. It is a contractual relation between the inventor and society: by granting to the inventor a temporarily limited monopoly, society would receive the greater good of the publication of the knowledge entailed. The separation of knowledge and commercial utility, therefore, is supposed to work out for the common good (under the aegis of the hidden hand of the market) (Etkowitz and Webster 1995).

And indeed, this came to be the general strategy of Celera Genomics as the sequencing race got under way. It would make its data public, but with a delay of three months for potentially lucrative annotations and sequences, so as to give its investors the chance to strike first. Coincidence or not, only two days after Venter's announcement to start Celera, the Wellcome Trust announced its decision to scale up the funding for the part (1/3) of the sequencing carried out at the Sanger Centre (Davies 2001). And shortly thereafter leaders of the genome project announced a change of course, namely the intention to complete a rough draft of the genome by 2001. This seemed to go against the strategy of a gradual up-scaling, but Francis Collins stayed the course. In 1999 the schedule for the rough draft was moved again, this time to spring 2000. One important strategy for speeding up was to channel more funding into the three most productive genome centres in the U.S., the laboratories of Eric Lander, Bob Waterston and Richard Gibbs (Davies 2001).

The draft version was published in *Nature*, 12. February 2001, at the same time as Celera published its draft version in *Science*. Celera thus made its map public, but it reserved the rights for the up-dates for paying customers. By the time, the company had filed more than the announced 300 patent applications, but it was retained that many of these were provisional, and that the final number would be under 300. The two publications sparked a new debate on the relationship between the two projects: Celera's version of the genome had used data from the publicly available HGP data bases in order to anchor its own sequencing data. Phil Green therefore concluded that "We are left with no idea how a true whole-genome assembly would have performed" (Green 2002). Hence, the discussion about the general status of the two maps continued, also after the official completion in 2003. Not unimportantly, the two versions contained differences, and due to the different approaches taken as well as the general climate between the two groups, it remains an open question to which degree a final synthesis could be negotiated. Adam Bostanci sums up:

"Finally, if all attempts to reconcile the two data bases fail and the sequences remain separate, it remains to be seen whether they will ultimately be used in different ways, one as a reference for basic research and public health, the other to satisfy the needs of pharmaceutical companies" (Bostanci 2004).

These differences will not be further elucidated here. On the 14. of april 2003, the completion of the genome project was announced. Its leader, Francis Collins, deemed it an unconditional success: "All of the project's goals have been completed successfully – well in advance of the original deadline and for a cost substantially less than the original estimates." (The International Human Genome Sequencing Consortium 2003). No doubt, according to the goals it had set for itself, the genome project had come through on many of its promises. It was assessed that the map corresponded to the sequence with an accuracy of 99.9 percent (Schmutz 2004). Hence, according to the interpretive premises laid down in this project, it is clear that the negotiation of the counterfactual organiser of the genome with its object, the sequence, was carried out with 99.9 percent accuracy.

However: Obtaining a static map of the genome is one thing; understanding how it works is another. Molecular biologists and geneticists have had their expectations cooled off by the shear complexity of the genome, which has turned out to be a different entity from the one projected in the 1960s and 70s (Fox Keller 2000). First of all there is the enormous amount of information that now waits to be interpreted. It was always understood that the genome project would have to be followed by such a phase, and that the data themselves would yield nothing as to biological function. That being the case, the increasingly unidirectional focus of the research community that it took to carry out the project may have been a two-edged sword. As made clear by Sydney Brenner in his Nobel Lecture from 2002, the strong focus upon sequence and data accumulation may even have come at the expense of the ultimate goal of understanding:

"We are all conscious today that we are drowning in a sea of data and starving for knowledge. The biological sciences have exploded, largely through our unprecedented power to accumulate descriptive facts. How to understand genomes and how to use them is going to be a central task of our research for the future. We need to turn data into knowledge and we need a framework to do it. So genocentric has modern biology become that we have forgotten that the real units of function and structure in an organism are cells and not genes" (Brenner 2002).

Hence, for the sake of practical applications of genomic sequence data, it is clear that the object "itself", which is not the sequence, but rather normal physiological function and pathological deviation from that norm, has still got a long way to go in order to be aligned

with its organising principle, the central dogma. In the article *Portrait of a molecule*, published as part of the 50 year anniversary of the central dogma, Philip Ball, like Brenner, directs our attention at the complexity surrounding the nucleus acids:

> "If all of this destroys the pretty illusion created by the iconic model of Watson and Crick, it surely also opens up a much richer panorama. The fundamental mechanism of information transfer in nucleic acids – complementary base pairing – is so elegant that it blinds us to the awesome sophistication of the total process" (Ball 2003).

And indeed, it is these processes that have come to constitute the further paths to be taken after the sequencing of the genome. Understanding the intricate workings of the interrelatedness of the many types of genes in the genome; understanding human genomic variation; the interrelatedness of genes and proteins, which has turned out a much more complex issue than first assumed by the "one gene – one protein" hypothesis, and the interrelatedness of proteins, to mention a few. New consortia have been established for those purposes, usually made up by joint public and private efforts. Some are the SNP Consortium, devoted to mapping DNA variations (Single Nucleotide Polymorphisms) among individuals (snp.cshl.org/); The HapMap Project, devoted to the understanding and mapping of complex diseases (www.hapmap.org/), and the Protein Structure Initiative, whose goal it is to "make the three-dimensional atomic-level structures of most proteins easily obtainable from knowledge of their corresponding DNA sequences" (www.nigms.nih.gov/psi).

7. The genome and the clinical context

In this chapter I start to discuss some of the challenges that may come from the developments described in the previous chapter. Considering that there are still uncertainties and areas of ignorance connected to the genome as a general physiological principle: what implications are drawn for the sake of exporting genomics to the clinical context, and which are the implications for legal and social regulation?

In keeping with Claude Bernard's definition of pathology as a deviation from normal physiological function, and taking into account the genomic turn, genetic disease may be defined as "disease caused by an abnormality in the functioning of an individual's genome"[60]. The clause about the genomic turn is important, because it is by no means granted that the average clinician will count him or herself as part of the "genomic era" (Guttmacher and Collins 2003). In Dorland's Medical Dictionary from 2003, genetic disease is defined in more conservative terms as "any disorder caused by a genetic mechanism", and the genome as such is not mentioned. This diversity of definitions may be interpreted as expressions of underlying political and scientific tensions resulting from the attempt to transfer genomics to the clinical context.

According to the traditional understanding, genetic diseases make up a rather small sub-species on the nosological chart. The main category is that of classical Mendelian traits, caused by one single gene (single gene disorders), like Huntington's disease, Hemachromatosis and Hemophilia (http://www.ncbi.nlm.nih.gov/). As already described, it was this class of diseases that came to be drawn into the molecular fold with the advent of genetic markers, and which came to make up the main goal of the gene hunts starting in the 1980s. Although the number of single gene disorders has increased along with these developments and the mapping of the genome, they only make up a small percentage of the more common diseases (Burke 2002). In addition come the chromosomal abnormalities, like Down's Syndrome and the other trisomies, known and studied since the late 1950s (Mueller and Young 1998). Last, but not least, we have the main category of diseases, multifactorial disorders, making up the overwhelming majority of known diseases, such as the cancers, diabetes, cardiovascular disease, hypertension and mental illnesses. These have traditionally belonged to a number of different disciplines in which the genetic component has not been

[60] http://www.medicinenet.com/genetic_disease/glossary.htm

particularly strong. This picture, say promoters of genomic medicine, is now about to change. As genomics research proceeds, results are transferred and integrated into general health care:

"Genomics has a broader and more ambitious reach than does genetics. The science of genomics rests on direct experimental access to the entire genome and applies to common conditions, such as breast cancer and colorectal cancer, human immunodeficiency virus (HIV) infection, tuberculosis, Parkinson's disease, and Alzheimer's disease" (Guttmacher and Collins 2003).

I bring a rather lengthy quote from one clinician in order to illustrate how the question of the definition of disease is also a reflection of institutional, disciplinary and economic issues:

Clinicians probably feel we have gone overboard in support of cell and molecular biology. I agree. With the exception of population studies, it is difficult for medical scientists to obtain support for research that clinicians find informative. Biomedical publications in journals with the highest impact factors, such as *Cell*, *Nature* and *Science*, deal almost exclusively with cells, molecules, and genes. In this rarified group, only the *New England Journal of Medicine* publishes articles of interest to clinicians. What is worse, impact factors now control academic advancement so that cell and molecular biologists are preferentially promoted within faculties of medicine. Once in positions of power, they are unlikely to renounce it to other groups. The control of medical faculties by scientists spawned and supported by granting agencies and multinational pharmaceutical companies is a feed-forward mechanism that threatens to maintain their power and to downgrade the importance of clinical practice in medical faculties in the future (Macklem 2003).

What is at stake here is the status of the genome as a global organisational principle, both as physiological discipline and as basic principle for health care reforms. From the point of view of many clinicians, it is not at all self-evident that the genome be made a, if not the, central object of clinical judgement: "Clinicians deal with diseased organ systems, not individual cells and molecules" (*ibid.*). According to this view, genomics should rather proceed as a continuation of genetics as a sub-discipline. However, there is no mistaking the ambition to overcome such opposition and to transform the knowledge base of health care systems according to genomic principles of normality and pathology:

"All public health professionals…will need an increasing appreciation for integrating genetic research, policy, and program development into their daily work. This is not different from the expected integration of genetics into health care in general and across the various medical subspecialities. Although recognising the need for a cadre of public health researchers and practitioners fully trained in genetics, we also believe that all public health professionals will be using advances in human genetics in research and practice. We do not particularly endorse the creation of a new public health subspecialty in genetics; rather we encourage and emphasise the smooth integration of genetics into public health practice" (Khoury 2000).

The molecular object in clinical use

A genetic test may be defined as "the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes[61] for clinical purposes" (Burke 2002). As can be understood from this definition, a number of genetic testing technologies are already in use in clinical practice. The tests take advantage of deviations from normal functioning somewhere on the continuum from DNA to protein, and the tests are deployed for a number of different purposes. Many tests are available that do not require more than a simple blood test of the patient in order to check for the presence or non-presence of disease markers, as for instance mass spectrometry (a technique that can be used to identify specific molecular substances). Other techniques may be invasive, like amniocentesis, in which tissue is collected from the fluid surrounding the foetus, or they may involve such techniques as sonography (hearing tests for newborns), or fetoscopy (a special stethoscope for listening to the heart of foetuses) (National Research Council 1983; Khoury 2003). Genetic *screening* is the application of genetic testing to an asymptomatic part of the population in order to single out specific genotypes associated with heightened risk for disease (*ibid*.). Hence, in contradistinction to individual tests, screening is carried out following general criteria such as ethnicity or age, whereas genetic testing applies to the individual and is typically related to clinical history or family history. However, many of the tests are the same or they are used in combination, so this is not a sharp distinction (Andrews, Fullarton et al. 1994).

Most of these tests are related to the so-called single-gene disorders and chromosomal disorders. The wide-spread use of tests for multifactor disorders is still an open issue that will be subject to disciplinary and institutional negotiations: the scope of the new tests will depend, among other things, upon their explanatory and predictive powers (Vineis, Schulte et al. 2001). I will return to this problem. For whereas that may be where the central point of discussion is today, the relevant regulatory mechanisms and institutions have emerged along with the screening tests for single gene disorders, and so that is where the exposition should start. I start out by giving a brief overview of the relevant tests and screening programs before I turn to a somewhat more substantial description of the policy issues that follow from the expansion of genetic tests. The main point is not to give a description of clinical practice, but to give an overview of the groups concerned by the projected transformation: from a limited set of genetic tests to a genomic medicine that potentially encompasses most aspects of

[61] The full chromosomal set of a cell.

medical care and health care. I concentrate upon developments within the American context, as that was where genetic testing was first introduced. Hence it was also there that the changes were first felt.

Newborn screening. The first screening techniques were introduced into prenatal care in the 1960s to test for Phenylketonuria (PKU), an error of metabolism causing too high levels of phenylalanine, an amino acid, in the blood of the foetus. Unless treated with a proper diet, the condition results in severe mental retardation (Walters 1998). Because the tests had not been properly evaluated prior to clinical application, serious problems turned up in practice. Among these were a high number of false positives, false negatives and unhealthy dietary measures. Along with PKU, hypothyroidism has been commonly screened for in newborns (Khoury 2003).

Prenatal diagnosis. Screening prior to birth was introduced in 1966, when chromosomal abnormalities/disorders were spotted in the amniotic fluid extracted from the uterus of pregnant women by the use of amniocentesis. Since that time, amniocentesis has been used to screen for markers in late pregnancies (*ibid.*). In the 1970s, certain neural-tube defects (spina bifada) were correlated with changes in proteins levels found in the blood sera of pregnant women (Walters 1998). Other diseases frequently screened for in newborns include cystic fibrosis and fragile X (Andrews, Fullarton et al. 1994). Chromosomal tests as well as developments within ultrasound technology have further expanded the horizons of prenatal screening, significantly to the spotting of Down's and the other trisomies.

Carrier screening is primarily directed towards people in the reproductive phase of life. In contradistinction to the above cases, these screening tests are not designed to make diagnoses, but to identify people at risk for passing on disease genes to their offspring. *Penetrance* is the concept used to express the likelihood (the risk) that a particular gene will be expressed, i.e. that the genotype will result in a changed phenotype (Collins 1999). In genetic disorders of particularly high penetrance, such as Huntington's disease, there is an absolute degree of certainty that the genotype will result in an altered phenotype later in life, and that the risk that the disease will be passed on to the offspring is 50 %. Huntington's disease is very rare, insofar as it is both dominant and monogenic. It is more usual to screen for recessive diseases: if both parents are carriers, the risk is that 1 out of 4 of their offspring will have the disease (Mueller and Young 1998).

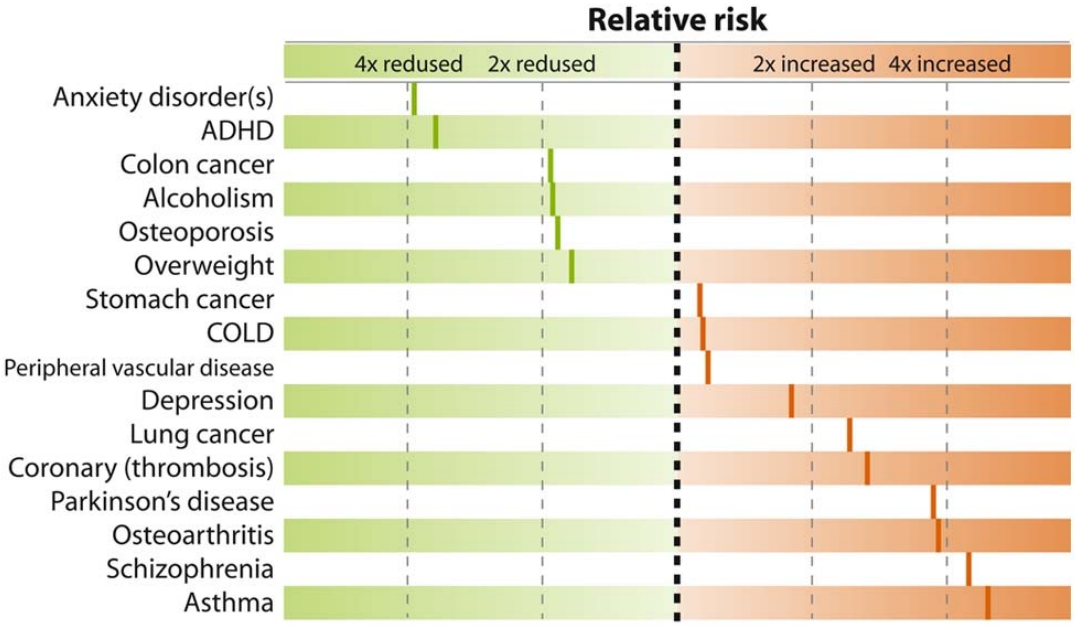
It has already been described how single gene disorders where mapped using a combination of genetic linkage maps taken from family studies and genetic markers. These early mapping projects were often directed towards specific populations, and so they resulted in the mapping of disease susceptibility in specific groups of the populations, typically specific ethnic groups. For instance, populations of Ashkenazi Jews have been demonstrated to be at risk for tay-sachs disease, people of Mediterranean origin are at risk for thalassemia, northern Europeans carry a heightened risk of cystic fibrosis, and people from northern Africa may have a heightened risk of sickle cell anemia (Burke 2002; Khoury 2003).

Genomic medicine: expanding the scope onto common diseases?

In the *genomic era*, these limited screening practices may find themselves expanded to the population at large, the goal being the determination of individual susceptibility to common, multifactorial diseases. In that way, it is surmised, disease may be prevented before it erupts (*ibid*.). Indeed, this expansion of preventive potential is perceived by many to be the main contribution of genomics to medicine (Burke 2002; Bell 2003; Guttmacher and Collins 2003). The application of the human genome map to individual cases of disease resides mainly in its potential for relating genotype variations of that individual to the common reference point established by the map. Between different individuals there is a genetic similarity of 99.9 percent. Individual variations occur within the 0,1 percent difference in individual's DNA that comes about as the result of different genotypes inherited from the parents, so-called heterozygosis (Guttmacher and Collins 2003). When two genomes are compared, the most simple of the resulting differences in base pairs are polymorphisms (SNPs) (Stoneking 2001). More complex differences will include differences in interactions between genes in different parts of the genome, so-called "haplomorphisms" (Guttmacher and Collins 2003). The HapMap project, a newly initiated cooperation between scientists from Japan, the U.K., Canada, China, Nigeria, and the U.S., is one heir of the genome project (www.hapmap.org/abouthapmap.html). In addition there is the program of proteomics.

If we are to believe the proponents of genomic medicine, changes to medicine and the health care system will come fast: "The rapid advances in human molecular genetics seen over the past five years indicate that within the next decade genetic testing will be used widely for predictive testing in healthy people and for diagnosis and management of patients" (Bell 1998), and, as argued by Guttmacher and Collins: following the sequencing of the genome,

genomic medicine is now ready to take "center stage in clinical medicine"(Guttmacher and Collins 2003). This brings us back to the scenario sketched in the beginning of this chapter, in which genomics replaces or penetrates the spaces of disease: the clinical domain, taxinomies and public perception. Five years after the article written in 1998, without any loss of faith, but with a somewhat more generous time-schedule, Bell writes that: "The discovery of the double helix half a century ago has so far been slow to affect medical practice, but significant transitions are likely to occur over the next 50 years" (Bell 2003).



In 10 or 20 years every patient may be presented with a risk profile for common diseases. The above schema is fiction, but it may become reality if the possibilities promised by genomic medicine come through. Reprinted with kind permission from Stefan Hjørleifson.

There thus seems to be some doubt, at least when it comes to the *timing*, regarding the implementation of genomic medicine. But there are other uncertainties as well. As argued in the previous chapter, there is at least reason for doubts concerning the relevance of some of the claims made by genomics. The question hinges on the general status of the genome: if it is indeed a unitary aggregate determining phenotype expression, chances are that that these can also be controlled through interventions with disease-causing genes. If, however, the number

of epigenetic and environmental factors influencing gene expression is great, then there is reason to doubt the general relevance of genomics to complex diseases. This was argued in an Institute of Medicine report from 1994:

> "Certain environmental factors may interact with only one set of genes and not with another. There may also be interaction between the various genes involved, so that the effects of multiple gene action cannot be predicted by separate analyses of each of the single genes. In such cases, definitive prediction will rarely, if ever, be possible. When dealing with genetic testing for some non-Mendelian diseases, it will be impossible to group individuals into two distinct categories – those at no (or very low) risk and those at high risk" (Institute of Medicine 1994)

In 2000, one of the authors of the 1994 report, Neil Holtzman, repeated and elaborated many of the same uncertainties. Now, the argument was published in an article written with Theresa Matheau for the *New England Journal of Medicine*, and the target was the alleged revolutionary potential stemming from the Human Genome Project. Revolutionary claims made by people like John Bell and Francis Collins "clothe medicine in a genetic mantle", the authors argued. Assuming that the penetrance of most common diseases, in contradistinction to single gene disorders, is generally very low, the authors questioned the relevance of genomics to clinical medicine. Due to incomplete penetrance there is no way of making strong correlations between genotype and phenotype when it comes to the most common diseases. Furthermore: where a genetic component is found to make up a decisive part of the aetiological picture, these incidences make up a small part of the cases only. This, it was argued, was the underlying reality of the genetics of Alzheimer's, type 2 diabetes, colon and breast cancer, in which the genotype had been found to account for less than 3 percent of the total number of cases. A similar critique was put forward in *The Lancet* in 2001 by Paolo Vineis, Paul Schulte and Anthony McMichael. There, it was argued that 1) for low-penetrance genes, the relationship between genes and environment is constitutive, and not a stable relation between two entities, 2) only highly penetrant mutations in cancer genes may act without interacting with the environment, and 3) there is an inverse relation between penetrance and the frequency with which a gene occurs in a population. The higher penetrance, the lower frequency; the higher frequency, the lower the penetrance (Vineis, Schulte et al. 2001).

There are already examples of genomic diagnoses yielding information about more complex diseases. One example put forward in replies to Holtzman and Matheau is hereditary hemochromatosis, in which more precise diagnosis has resulted in improved possibilities for

therapeutic responses (Block and Aulisio 2000; Khoury 2000). Advances has also been made with certain types of cancer, significantly breast, ovarian and colorectal cancer (Emery and Hayflick 2001). But the question remains whether these results can be generalised to other cancers or diseases. Questions also remain concerning the predictive value of some of these tests. Although the gene for breast cancer has been singled out as a potential target in screening programs as early as 1999, this does not automatically mean that the test will yield a positive "net outcome" in terms of predictive value: "we can assume that, for complex phenotypes with a genetic architecture that involves dozens if not hundreds of loci, many variants will be involved and they will be sorted into individual packages with as much variety as personality and physiognomy" (Cooper and Psaty 2003).

The presuppositions of genomic medicine can be related to more philosophically oriented analyses of probability. John Maynard Keynes, in his one philosophical work, *A Treatise on Probability,* articulated the principle of *limited independent variety*, stating the general presupposition that the field about which we are making predictions is not infinitely complex, but can be restricted to a limited number of cofactors. The principle "assures us that the objects in the field, over which our generalisations extend, do not have an infinite number of independent qualities; that, in other words, their characteristics, however numerous, cohere together in groups of invariable connection, which are finite in number", quoted from *The Oxford Dictionary of Philosophy*.

Many developments may be imagined to overcome the present doubts concerning genomic medicine. Some of these have already been mentioned in the previous chapter:

One strategy would be to wait for the accompanying results of proteomics. The true value of genomics, writes Claude Lefant, lays in its being coupled to proteomics: "that is the tool that will lead to the understanding of pathological processes at cellular level" (Lefant 2001).

New maps will arise of the gene complexes (allegedly) responsible for complex diseases. These will come about by assigning SNPs to so-called "haplotypes", larger DNA segments containing more alleles that are all inherited together (Guttmacher, Collins 2002). New technologies, not the least in bioinformatics, will have a huge role to play along with the further developments of complex systems theories. But also within these "revolutions" the

question of the unity and controllability of the genome will loom. The question is not if new discoveries will be made or if developments will take place, but rather how significant their impact will be on clinical medicine.

But how do we know that these developments will not *add*, rather than overcome complexity?

Arguments like the above share a weakness with many optimistic views about the value of genomics: not only do the therapeutic and diagnostic rewards lie in the future, -the same goes for the basis of evaluation. In the vocabulary of the social sciences: they see the creation of social order as a mainly scientific, not a social problem. The (radical) expansion of genomic medicine is predicted on technical developments and not on what is known to work clinically *today*: "While it is true that the future may not be a linear projection of the past, the claims of genomics still have to be evaluated on the basis of principles that we currently accept as valid" (Cooper and Psaty 2003).

Taking these distinctions seriously, Cooper and Psaty argue, grants for genomics (or proteomics for that sake), a very limited role at the moment. In choosing such a line of argument, thy not alone: both proponents and sceptics of genomic medicine advice that developments be made at a slow pace so as to integrate all involved parts, from the general physician to the patient, the ethicist and the wider public. Information without communication makes for a bad strategy of implementation. Developments must move slowly in order for integration to take place and in order to be followed by a proper clinical evaluation. (Emery and Hayflick 2001; Knottnerus 2003). At the outset, very few would declare themselves opponents of such an approach.

And so we are left confused on a slightly higher level. The problem is, of course, that even with this consensus established, it will be subject to widely differing interpretations: sceptics may argue that a lid be put on the "gene talk" until more is known (Holtzman and Marteau 2000; Vineis, Schulte et al. 2001; Cooper and Psaty 2003; Porta 2003; Kerruish 2005); optimists will argue that we have to start transforming the health care system today (preferably yesterday) in order to be prepared for technological developments that will inevitably come (Emery and Hayflick 2001; Bell 2003; Guttmacher and Collins 2003; Knottnerus 2003; Khoury 2005).

Therapy?

The main rationale, we may state, behind the application of genetics to the clinical context, is its potential for discerning the exact mechanisms involved in pathogenesis (Bell 1998). This will also entail the ability to make more exact diagnosis and to intervene with the specific disease causing mechanisms:

> "The issue of specificity of treatment is an important one. New genetic tests to assess the risk of common diseases are likely to have properties similar to those of tests for factor V Leiden. They will identify relatively common genetic traits that interact with other genetic and environmental factors to increase risk. Their clinical usefulness will depend on the ability of specific, effective interventions to reduce risk" (Burke 2002).

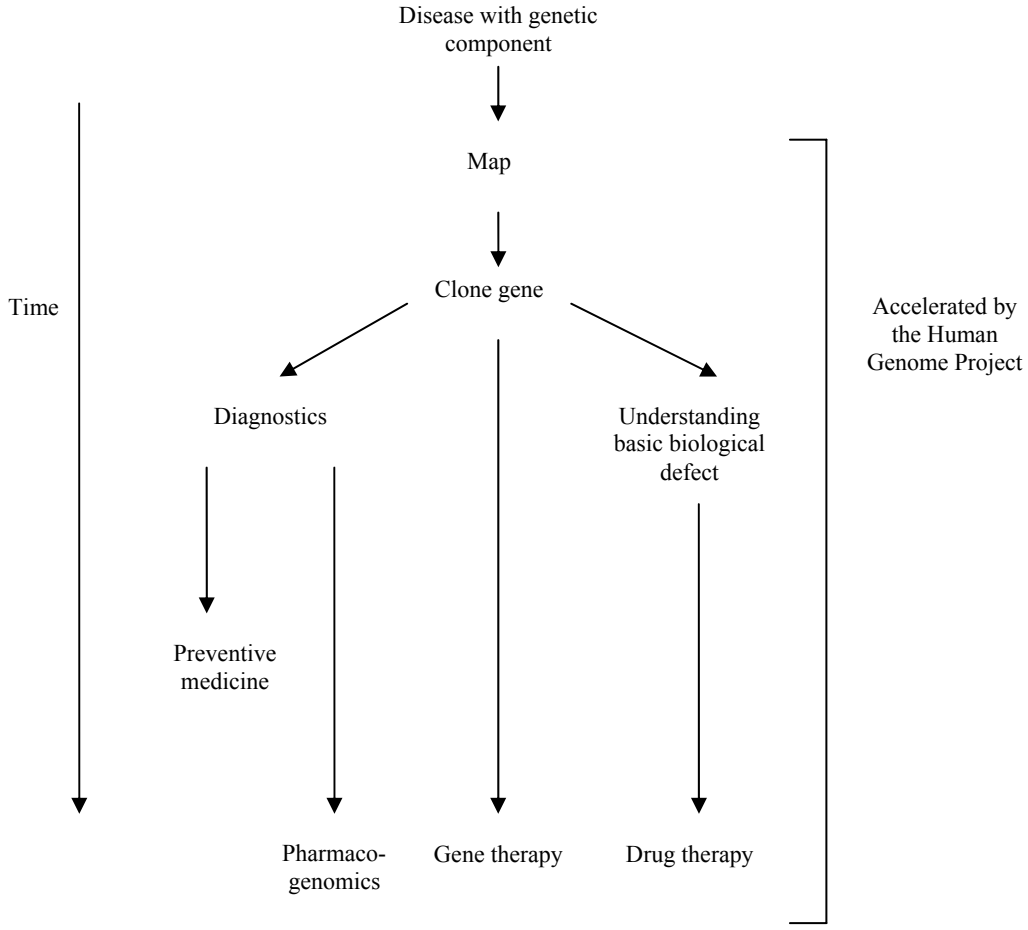
So far, the case for direct intervention, so-called gene therapy, has been relatively weak. Gene therapy is a direct intervention with the disease-causing gene in which the gene is replaced with a healthy one. Although successful gene therapy trials have taken place (Petit-Zernan 2002), the revelation that experimental trials on a boy in Paris had caused cancer caused a stir in the world of clinical genetics. The approach remains experimental, its long term effects unknown, and regulatory responses in different countries vary (Check 2002). The main difficulty is the precise targeting of the therapeutic agent, which has so far been relying upon vectors that are hard to control when inserted into the host.

For the foreseeable future then, options for therapeutic action remain mainly within the diagnostic and preventive domain: gene expression profiling to obtain more precise diagnoses, genotyping in order to adapt drug treatments to the individual patient and new drug therapies and so on. Guttmacher and Collins does not see that this will change within the near future:

> "Since it remains difficult to alter genes in humans (for both technical and ethical reasons), for the next couple of decades we will generally use personalized modifications of the environment, and not of genes, to translate genomics-based knowledge into improvements in health for most of our patients. Clinicians will much more frequently suggest to patients with hereditary hemochromatosis that they avoid iron supplementation than that they consider gene therapy" (Guttmacher and Collins 2003).

The occurrence of individualised and preventive genomic health care for everybody is predicted on the development of better and more cost-efficient technologies, ultimately issuing in the "$1000-genome", the sequencing of the individual patients genome within a decade or two (Guttmacher and Collins 2003). However, the authors see one serious obstacle to this progression of events: "Unless complex issues regarding the patenting and licensing of

gene-based knowledge and techniques are dealt with more successfully than they are today, the "$1000-genome" will remain a wish, not a reality" (Guttmacher and Collins 2003).



The genomic revolution in medicine as projected by Francis Collins. So far the main outcomes of genomics have taken place mainly according to the arrows at the left in the diagram. Copied from (Collins 1999).

Co-developing policy issues

At this stage I would like to prepare for a subject that will be treated in more length in the later chapter on patient autonomy. That is the regulatory issues that co-evolved along with the developments sketched in this chapter. At the more analytical level, it is also the beginning of the story of how the organising principle of autonomy made its way into the clinical application of genetics.

U.S. health authorities recognised early on that there was a need to regulate the new and fast expanding field of genetic testing and screening. In what follows, I describe some central policy issues that developed along with the screening programs. I do this mainly by recounting some central issues from three policy documents: "Genetic screening: Programs, Principles and Research" (National Academy of Sciences 1975), "Screening and Counselling for Genetic Conditions" (National Research Council 1983) and "Assessing Genetic Risks, Implications for Health and Social Policy" (Institute of Medicine 1994). Many of the same people, scientists, physicians and ethicists, served on the committees, and so the continuity between the three reports is strong (Walters 1998).

During the early 1970s, as recombinant DNA technology and genetic screening programs were emerging as significant social factors, the field of bioethics was establishing itself as a discipline relevant to policy-making. Apart from the biohazard debate surrounding recombinant DNA, genetic screening programs were particularly amenable to ethical analysis. In 1972, a group from the Hastings Center led by a theologian, James Gustafson, and a scientist, Richard Roblin, published a report in the *New England Journal of Medicine* on "Ethical and Social Issues in Screening for Genetic Disease" (Jonsen 1998; Walters 1998), 256. At the same time, on the request of the American Society of Human Genetics, a committee was established by the National Research Council to evaluate screening practices. As mentioned, sloppy routines and premature methodologies in PKU screening was one reason for assessing the situation. Similar deficiencies seemed to haunt other screening programs as well: Following the successful implementation of carrier screening programs for tay-sachs disease in the Ashkenazi Jew community a similar program for sickle cell disease had been introduced to communities of Afro-Americans. The programs, made mandatory in thirteen states, were badly targeted: Aimed at preschool children (!), marriage licensing and school admission, and rarely followed up by proper counselling, the message more often than not came through as badly distorted. Allegations of discrimination and stigmatisation followed, and soon the mandatory character of the programs was abolished (Jonsen 1998). Episodes like these singled out the field for ethical analysis, and so many of the members from the Hastings group were taken aboard the NRC committee.

Initially established to investigate the practice of PKU screening, the Committee for the Study of Inborn Errors of Metabolism soon found its mandate expanded (by the NRC) to deal with screening in general:

"Screening programs for genetic diseases and characteristics…have multiplied rapidly in the past few decades, and many have been begun without prior testing and evaluation and not always for reasons of health alone. Changes in disease patterns and a new emphasis on preventive medicine, as well as recent and rapid advances in genetics, indicate that screening for genetic characteristics will become more common in the future. These conditions, together with the mistakes already made, suggested the need for a review of current screening practices that would identify the problems and difficulties and give some procedural guidance, in order to minimize the shortcomings and maximize the effectiveness of future genetic screening programs" (National Academy of Sciences 1975).

Although recognising decisive shortcomings in screening practices so far, as well as the many uncertainties connected to expansion, the potential for development according to improved standardised and scientific rules was underlined. However, it was important that the many possible side-effects on the social order were taken into account, and that one proceeded in "an experimental mood" (*ibid*.). A main conclusion of the ensuing report was that screening be made voluntary, not mandatory. *Public participation* was pointed out as incremental to the successful implementation of screening programs. Screening practices are unique in the sense that clinical treatment and research are necessarily connected: because there is no permissible way of studying human inheritance in laboratories, the only way to get at human genetic variation and its phenotype expressions is to study it *in vivo*. Future programs, therefore, would have to proceed in ways strongly integrated with the particular societies or groups that were studied, as well as with local authorities and social organisations involved. For achieving these goals it was essential that the purposes of the programs were clearly articulated and that the relevant knowledge of genetic disease was spread in the population. Hence, it was also very much a matter of *educating* health professionals as well as the general public in matters genetic. This would have to take place in medical faculties, in the education of health professionals, but also, importantly, in the public school system. All in all, an integrative approach was sought out, what Sheila Jasanoff call a strong co-production of social and scientific order (Jasanoff 2004). Furthermore, integration was to take place within the wider framework of health care development: "In the future, genetic screening should be regarded as one among several preventive health measures and its development should take place in the context of the evolution of health care in general" (National Academy of Sciences 1975).

A number of *legal* issues were also introduced, significantly the question as to whether screening be made mandatory or not. The committee recommended against such measures, arguing strongly in favour of the necessity to keep with a voluntary approach. In keeping with

the above sketched approach, also the legal matters should be integrated into a wider set of social, ethical and psychological concerns:

"Screening authorities should consult regularly with lawyers and other persons knowledgeable in ethics to avoid social consequences of screening that may be damaging. These take the form of invasion of privacy, breach of confidentiality, and other transgressions of civil rights, as well as psychological damage resulting from being "labelled" or from misunderstandings about the significance of diseases and carrier states" (*ibid*.).

These problems were further elaborated in a study published in 1983 that specifically addressed these issues from the "ethical, social and legal" points of view. The report, issued on the request of Congress, carried the somewhat intricate title *Screening and Counselling for Genetic Conditions: A Report on Ethical, Social and Legal Implications of Genetic Screening, Counselling and Education Program* (The President's Comission 1983). The first thing to notice here is the introduction of a novel institute on the interface between human genetics and society, namely that of genetic counselling[62]. The genetic counsellor was there to help people making difficult decisions about genetic choices by supplying the relevant information:

"Genetic counselling helps people with a potential or manifest genetic problem understand and, if possible, adjust to genetic information; when necessary it aids them in making decisions about what course to follow. It is an individualized process in which a specialist in medical genetics confers with an individual, a couple, or sometimes a group seeking additional information or assistance" (*ibid.*).

The second thing to notice is that ethical, social and legal dimensions are singled out as distinct issues worthy of their own report, and in demand of distinct expertise. Although in many ways continuing the integrative approach of the previous report, it is clear that the second report simultaneously implied an out-differentiation of disciplinary relations. This also meant a re-conceptualisation of some of the central issues of the 1975 report. Centrally, the issue of voluntary participation now came cloaked in a new language:

"The Commission believes that the principle of autonomy, which holds a high place in Western ethical and legal tradition, is important not only in the relationships of individual patients and health care professionals (through the requirement of informed consent) but also in the choices that people make about the uses of genetic services" (*ibid*.).

[62] Genetic counselling existed already in the 1960s (Jonsen 1998). My point is that it is introduced as a means for policy-making.

The notion of informed consent, stemming from a court decision in 1957, had also been included in the report from 1975. It entailed the notion that the patient be made familiar with the possible consequences of obtaining genetic information prior to the giving of such information. But its derivation from the primary principle of autonomy was a new construct that resulted from the use of ethicists and philosophers in the committee (Jonsen 1998).

What was more: the principle of informed consent (hence also autonomy) was expanded, from regulating the participation in screening programs to include the relationship between the patient and the physician or genetic counsellor *and* policy-making. This novel construction (in a medical context) was seen to form part of a whole, expressed in a principle-oriented approach. Four principles emerged as decisive: autonomy, beneficence, justice and privacy. The concepts of autonomy and informed consent came to establish a new contract between the concerned groups: geneticists, counsellors, ethicists, patients and policy-makers. The early screening programs suffered from a lack of clearly stated goals and operational guidelines, both ethical and scientific. For instance, the issue of mandatory screening resulted in significant problems on the interface between the health care system and the communities that were enrolled in the programs. There was a clear need to protect the citizens/patients from undue intrusions of the medical system, and patient's rights seemed to secure a good approach. On the side of the policy-makers, specific principles and guidelines were amenable to be made operational and as such served to order a seemingly chaotic field.

And the ethicists? In a post-metaphysical age, they found a field of practical relevance for their theories. As claimed by Stephen Toulmin: "medicine saved the life of ethics" (Toulmin 1982). As will be seen in the later chapter on law and bioethics, this approach to decision- and policy-making would be decisive, not least through the work of bio-ethicists Tom Beauchamp and James Childress. The significant outcome of these developments was that the issues of screening, counselling and autonomy were seen to form a coherent whole:

> "In sum, the fundamental value of genetic screening and counselling is their ability to enhance the opportunities for individuals to obtain information about their personal health and childbearing risks and to make autonomous and noncoerced choices based on that information" (The President's Comission 1983).

Before continuing, the issue of noncoercion alluded to by the committee should also be remarked upon. It was noticed that the basis for making genuinely autonomous choices in

matters genetic could be threatened by "subtle social pressures": the indirect influences from health personnel and social expectancies arising along with the new screening possibilities. For instance, a parental couple that does not use the opportunity of genetic screening and counselling and thereafter has a severely retarded child may feel themselves responsible for not having avoided that outcome. However, the committee did not come up with much in the way of recommendations for avoiding such undesired side-effects, except from underlining the necessity of educating the public.

The principle of "non-directedness" in genetic counselling was put forward as one important requirement in order to secure that the counsellor remained objective and did not intrude on the domain of the decision-maker, the patient. Indeed, screening and counselling *were* the means by which to prevent such effects, and as such more of a solution than part of a problem. Alluding to the pluralist culture of the United States, it was therefore concluded that

> "Nowhere is the need for freedom to pursue divergent conceptions of the good more deeply felt than in decisions concerning reproduction. It would be a cruel irony, therefore, if technological advances undertaken in the name of providing information to expand the range of individual choice result in unanticipated social pressures to pursue a particular course of action" (*ibid.*).

In 1994, a new committee was established, in part consisting of old members from the 1974 and 1983-committees. This time, however, there was not an exclusive focus upon ethical and legal issues. The main goal was to investigate the role of risk assessment in screening and counselling, and to draw implications for health and social policy. The report started out by quoting and reiterating the point made in 1975: screening programs were spreading and regulatory and ethical measures were lagging behind. The ethical principles from 1983, however, were incorporated into the general framework for assessment and policy-making: "The committee's fundamental ethical principles include *voluntariness, informed consent, and confidentiality*, which in turn derive from respect for autonomy, equity, and privacy" (Institute of Medicine 1994)

One of the main reasons for re-assessing the situation was the rapid expansion of genetic tests for a rising number of diseases. These were, of course, direct results of the explosion of discoveries in disease-causing genes. But with these developments in mind, the purpose was also to address the further expansion of such tests, possibly also to more common diseases of

higher aetiological complexity, possibilities that would come from the Human Genome Project (*ibid*.).

8. Recasting the subject

I will now resume some of the stories told in the previous two chapters and relate them more explicitly to the methodological framework laid out in chapters one to three. The purpose of that exercise is first and foremost to gain some reflective distance to the analysis of the gene, and to try and place it within a wider socio-historical context. After that I will return more explicitly to regulatory questions and science policy.

Towards the end of the chapter on Heidegger I specifically concentrated on two elements in his philosophy, that of *Gestell* (for which an inaccurate but useful translation may be "framework") and that of *Bestand*, or the "standing-reserve". I then used these as clues for the elaboration of the more sociological oriented terms of the counterfactual organiser and the techno-medical object. The counterfactual organiser is similar to the conception of *Gestell* insofar as it serves as a general conceptual, instrumental and perhaps also institutional framework (i.e., by introducing the counterfactual organiser, I specifically imply institutional dimensions).

In order to escape Heideggerian ivory-tower philosophising, the two following features must be underlined concerning the counterfactual organiser: 1) it is a communicative strategy, insofar as it makes possible the inter-subjective sharing of data as well as common, standardised ways of acting and talking in the community of researchers; 2) it makes presuppositions about causal relations in the world, and it may therefore be directly relevant to experimental, clinical and social action. It is through mechanisms like these that the counterfactual organiser is capable of establishing itself not only as a scientific principle, but also as social metaphysics. It does not come floating through the mist of history like some mystic entity, like "Epochal Being" or anything similar.

Furthermore, Heidegger did, quite understandably, proceed according to the world-view of physics. Hence, *Gestell* is primarily conceived of in terms of Newtonian physics, or at least something very similar. *Gestell* comes about as the result of a mathematical projection, through which nature is reinterpreted on an a priori basis of geometrical space. Although the attempts at reducing molecular biology to physics have made up a substantial part of its tradition[63], such a model is barely valid as a representation of the ways in which molecular

[63] James Watson, for instance, has always emphasised the direct line between the work in Max Delbrück's phage group, of which he was a part, and his later work. The fact that Delbrück had been a student of Niels Bohr was

biologists think and work. There are, in principle, no limits to how far we can precede in our search for a basic level: the nucleotide bases of DNA are themselves made up of atoms, protons, neutrons, and so on. But the reduction of the organism to its single parts comes at a price: "an organism can be made the object of physics, but the more detailed knowledge we obtain, the more we suppress the organism itself" (Fjelland 2001).

As stated by Richard Burian: "In brief, molecular biology is less like Newtonian mechanics than it is like auto mechanics: What it studies are *mechanisms* and it *uses* those mechanisms to intervene in nature" (Burian 1996). In Burian's view, molecular biology contains no general laws, not even the central dogma would qualify as a law in the sense ordinarily attributed to the concept in physics. Its heavy reliance upon the use of model organisms, its traditionally strong reliance upon experiment, and its reluctance towards formalistic approaches are all expressions of this.

We have seen how molecular biology gradually, in the1960s, came to encompass other disciplines, significantly biochemistry and embryology. With the coming of recombinant DNA technology and mapping and sequencing technologies in the 1970s and 1980s the discipline grew even stronger, and came to encompass at least one medical and clinical discipline, human genetics. But today, it may seem that the space of development that was closed in the 1960s is again opening up to the wider field of biology. The one-dimensional space of the central dogma and the genetic code may not suffice to explain biological function on all of its many levels: protein folding, cell and organ function, not to speak of the organism as such. Genomic function is not enough: "it is only in the context of higher level structures, functioning properly, that molecular mechanisms operate "correctly"" (Burian 1996). In Burian's view, molecular biology has come to rely, not upon a central theory, but rather upon "an immensely powerful battery of techniques for getting at the interrelated families of complex mechanisms found in all sorts of organisms" (*ibid*.).

What this indicates is that molecular genetics may emerge not so much as *the* basic discipline of the life sciences, as a way of communicating about biological function on different levels. In a philosophical language, it may emerge as more pragmatic and case-based than the unitary

later used to establish the scientific authenticity of the phage group by aligning it with the Copenhagen school (Abir Am 1999). Watson has later (1994) been quoted as saying "There is only one science, physics: everything else is social work" (Rose 1997: 8).

and deductive ideal taken from physics. On this model, a strict genetic determinism is an impossibility: between each level of biological functioning, DNA, protein, cell, organ, and so on, there is a gap that cannot be bridged without losing sight of function and organisation on at least one of the levels. Each level of organisation is *emergent*: "emergent explanations are holist insofar as they are irreducible to the behaviour of component parts" (Fox Keller 2002:284).

So much for the philosophy of biology. It may give us a clue for interpreting the theoretical framework of molecular genetics, but it does not put many restrictions upon the ways in which genetics is actually conceived and applied. We may, however, keep the notion in mind that whereas molecular biology in the 1960s emerged as master discipline along with the master molecule, today the somehow paradoxical situation exists that the success of the genome project has led to the necessary implementation of a wider spectre of disciplines. And so it is that an evolutionary biologist, without causing any stir, today may write that:

"It is important to note that genomes are only one of many important levels of biological organization, and that genomic data are only truly useful when viewed in the context of morphological, cytological developmental, physiological, and ecological information. By itself, the possession of even a complete genome sequence does not provide any great insight into the workings of living systems, let alone the place or essence of humanity" (Gregory 2005).

The place and space of the genome is still being negotiated. Indeed, on a social and institutional scale, that *is* what post-genomics are all about: working out the (functional) implications and meanings of enormous sets of dis-embedded, perhaps even de-biologised, information.

Turning to the *clinical* context, proponents of genomics do tend to conceive of the genome as a unit, and not as a bundle of unrelated DNA. We may accept this, but still be more or less in the dark as to the practical implications of this. What does it *mean* to conceive of physiological function and pathology on the level of DNA?

Again, a number of possibilities are available:

As a *minimal consensus*, it can be assumed that the central dogma poses a valid approach to the *interpretation* and *understanding* of that unit called the genome for general physiological understanding, while not denying the validity *and necessity* of other approaches (Sarkar

1996). This would be a version of genomics that sought to encompass some of the doubts regarding the allegedly unique status of the genome. As already seen, we do not even have to leave DNA before we get to epigenetic factors, namely the chromatin in which DNA is wrapped. In addition, large parts of the genome has functions that are still unknown, like "junk DNA"; and phenomena like alternative splicing have forever falsified the notion that one gene makes one protein. Thus, the move from genetics to genomics can be said to encompass a move in a non-reductionist direction, insofar as function is conceived in terms of the interrelatedness of the genes that make up the genome. This much is of course recognised also by the proponents of genomic medicine (Guttmacher and Collins 2003).

In many cases, however, a stronger supposition is also made, namely that the tools of molecular genetics are sufficiently powerful to *explain* development on a more basic level than other disciplines, and, even stronger, to use its models to *predict* development (Burke 2002; Bell 2003; Guttmacher and Collins 2003). Obviously, the main rationale for introducing genomics into medicine will be its potential for revealing disease mechanisms so as to increase the power to diagnose, prevent and cure. On this stronger account of physiological function, the central dogma is, if not exactly taken as a general law of nature, then at least to be sufficiently universal to count as such. In other words: genomic information leaves us with a surplus of alternatives for action that we did not have before. In a sufficient number of practical cases, there is a sense in which phenomena on a higher level of organisation may be attributable to genotype. The genotype turns out a better basis for diagnostic, preventive or therapeutic action than the phenotype, the clinical appearance. This alternative has, to some extent, already been pointed to and discussed in the previous chapter. In addition to findings already made in human genetics (mainly single-order diseases but also some heterogeneous), it also places great faith in the heightened possibilities that will come from developments within fields like bioinformatics, mathematics and complex systems theory (Fox Keller 2002; Guttmacher and Collins 2002).

As these issues cannot yet be settled, I will contend myself with the following "conclusion": the space of physiological development and the institutional settings in which it unfolds are still open and under constant renegotiation. The outcome of the "genomics revolution" is uncertain, and there is a wide space for interpretations and visions of the future. The social and ontological status of the central dogma (in its genomic clothing) and the gene as a material object is still a matter to be settled. Presumably, this will not take place *tout court*,

but rather be a matter of differing developments within differing fields. For instance, the epidemiological information yielded by genomics may turn out useful whereas therapies continue to lag behind. The universality of the genomic object will be measured in practical terms by it's capability of organising standardised practices of diagnosis, therapy and prevention.

I now turn to consider some of the historical and sociological conditions under which these negotiations take place. However, it is important to note that in so doing, I remain with the hermeneutic conception of the scientific and technological object. It is not a macro-sociological interpretation, but an exposition of the ways in which we *act* and organise our actions by manipulating and interacting with the social and the material. I do, however, rely upon Ulrich Beck's interpretation of reflexive modernity (qua *Zeit Diagnosis*) as a way of getting at the wider, socio-historical setting.

The genome between first and second modernity

In at least three important senses, the genome emerges as the social and material realisation of age-old visions of modernity. In order to demonstrate this, I relate the genome as envisioned by its contemporary proponents to central elements in Descartes and Bernard. Some of the generalisations that follow may not be to the taste of some historians and philosophers of medicine. I repeat that the whole analysis is carried out from a specific methodological point of view. I remain with the hermeneutic interpretation of social action rather than, say, the French epistemological school. As I see it, the particular advance with a hermeneutic approach is its ability to remain close to the perspective of action and the everyday perception of the world. I freely admit to extrapolating the present onto the past, in the sense that I focus on the relevance of past intellectual and institutional developments as they may cast a light upon present-day genomics, and not (primarily) as they may have appeared to the actors at the time. It is an interpretation of modern medical action in terms of the gradual replacement of traditional knowledge by a rational and scientific basis. It is therefore also a short history of the counterfactual organiser.

First of all, the genome may be interpreted as the physiological realisation of the Cartesian and Galileiean outlook on the body and the physical world. It is the attempt to isolate and cleanse the basic causal mechanisms of the body from unwarranted and subjective influences:

"Common diseases are currently defined by their clinical appearance, with little reference to mechanism. Molecular genetics may provide the tools necessary to define diseases by their mechanisms" (Bell 1998). The mechanism referred to here, is described as the genotype, the clinical appearance is the phenotype. The clinical appearance, it is argued, disturbs the clear and distinct perception of the genotype, the underlying disease mechanism: "An understanding of the genetic basis of maladies is providing a new taxonomy of disease, free from the risk that the diagnostic criteria related to events are secondary to the disease process, rather than its cause" (Chakravarti and Little 2003). The similarity to the aforementioned primary and secondary qualities of Descartes and Galilei is striking: today, primary qualities may be reinterpreted as genotype whereas the secondary qualities are the phenotype (see chapter one).

Furthermore, we recognise the attempt at establishing the taxonomy of disease on a firm, scientific ground. This was not undertaken by Descartes, but rather by the Paris clinicians. During that process, the distinction between primary and secondary qualities emerged in a clinical context, in the conceptual guise of the *sign* and the *symptom*. The sign was correlative of the objectifying "gaze" (Foucault) which again found its place within the newly established clinic. The clinic was the first attempt to establish a scientific knowledge base for medicine and for the taxonomy of disease; hence it may also be termed the first modern medical institution.

Still, clinical practice did not emerge as properly "modern" until the establishment of physiology through the intermediary of experimental medicine: pathology is the deviation from normal, physiological function. Normal physiological function can only be established through experimental intervention (Bernard 1957). Furthermore, there is an internal dialectic between the clinic and the laboratory, in which the laboratory is to serve the knowledge base for clinical action. The laboratory stands in the service of the clinic, but epistemologically speaking the laboratory is the master. Again, we see the intention of replacing the old knowledge of disease with a new, more precisely defined, scientific conception of disease.

Claude Bernard articulated this program, but he did not live to see it carried out in practice. In spite of differences to the Bernardian program[64], the bacteriologists and immunologists *did*

[64] I.e., they did not place the cause of disease in the internal milieu, as did Bernard, but in the external environment. Øyvind Michelsen pointed this out to me.

carry out the program of experimental medicine on a broad social and institutional basis, insofar as the experimental activities of people like Robert Koch, Louis Pasteur and Paul Ehrlich managed to establish a knowledge-base that also entailed the effective manipulation and distribution of the techno-medical object on a broad basis. For the first time, experimental physiology translated directly into clinical application. *Specificity* emerged as a main organisational principle of both scientific and medical activity, first articulated in terms of toxins/antitoxins, then as antigen/antibody, and these were finally encapsulated within a general paradigm of *protein specificity*, which was successfully applied to a number of biological and physiological disciplines (Mazumdar 1995; Kay 2000). As described in the section on the gene, in the late 1950s/early 1960s the organiser of specificity translated into that of *biological information*. Hence, there is a definite rationale for arguing the influence of immunology on later research in genetics and genomics: the success of specificity as a counterfactual organiser was translated into that of biological information.

In a strong interrelation to this conceptual transition was the powerful institutional position from which the relationship between experimental and clinical action emerged in the wake of the therapeutic revolution. As argued by Erwin Ackerknecht:

"The consequences of the development of bacteriology were tremendous. It is impossible to overemphasize the importance of the fact that for the first time in history *causes* of numerous diseases became known. The way was opened for a replacement of symptomatic or empirical treatment by causal treatment or prevention. A definite answer could finally be given to the question as to whether the disease-producing agent was a "miasma", a chemical agent or a living organism. The problem of the specificity of diseases was solved. The gap between the discoveries of pure science and their successful application in practice was bridged faster than ever before. This fact impressed the lay public with the potentialities of medicine more than any previous discovery. Rational treatment and prevention of infectious diseases became possible on an unprecedented scale. The whole of medicine was transformed, with the fields of public health and surgery undergoing a complete rejuvenation" (Ackerknecht 1982:183-184).

And, as argued by Roy Porter, there were only two disciplines in the 20th century that could show for them selves the same interaction between experimental and clinical science: "The nexus of basic science, clinical research and practical medicine has been notable in two fields in particular in the latter half of the twentieth century. One is genetics…The further field of spectacular development during recent decades has been immunology" (Porter 1997:586 - 589). Porter also serves some hints as to the historical interrelations of the one to the other:

"Basic research, clinical science and technology working with one another have characterized the cutting edge of modern medicine. Progress has been made. For almost all diseases something can be done; some can be prevented or fully cured. Nevertheless, a century which has brought the most intense concentration of attention and resources on medical research ends with many of the major killers of western society – particularly heart and vascular disease, cancer, and chronic degenerative illness – largely incurable and in many cases increasing in incidence. It can be argued that one reason why there has been relatively little success in eradicating them is because the strategies which earlier worked so well for tackling acute infectious diseases have proved inappropriate for dealing with chronic and degenerative conditions, and it has been hard to discard the successful 'microbe hunters' formula" (Porter 1997, 595).

Hence, I take it that genomic medicine is indeed chasing the "microbe hunters formula", and that the therapeutic revolution of bacteriology and immunology in important ways, scientifically and institutionally, have shaped our present expectations of medical progress.

Obviously, there are differences. Although I have referred to the therapeutic revolution as taking place according to Bernardian prescriptions, this is not entirely true. The therapies developed by bacteriologists and immunologists resulted from the discovery and isolation of specific micro-organisms; it did not come from a prior establishment of basic physiological mechanisms. That stated, according to Paul Ehrlich's receptor immunology, disease could indeed be seen as a deviation from the normal function of cell receptors, which was the uptake of nutrients at the cell surface (Silverstein 1989). But this may have been more of a post hoc speculation than it was of experimental physiology in Bernard's sense. Indeed, Ehrlich's attempt to establish a general theoretical framework for his findings (the side-chain theory) marked the beginning of a retreat from clinical relevance, a descent into "the dark ages of immunology" (Silverstein 1989). Where theory formation in immunology came almost as a result of practical and clinical application, this has not been the case with genetics, in which theory formation and experimentation has been under way for more than fifty years.

However, if the attempt to establish the human genome at the centre of physiology, medical practice and health care should succeed, one could argue that it would be the first successful application of Bernard's vision of modernised medicine. The genome would make up, as argued by Francois Jacob in 1970, the "hidden design" of physiological function.

I have outlined several characteristics that mark the genome as a typically modern object: the attempt to cleanse knowledge of all uncertainty and irrelevant influences through finding a secure first principle, the related wish to establish a new taxonomy of disease based on scientific principles, and the direct relevance of experiment to clinical application.

However: if we are to believe a wide number of observers of the technological condition, we do not any more find ourselves in the modernity of the 19th century; neither that of the first 2/3s of the 20th century. We are "post industrial" (Bell), "late capitalist" (Habermas), "postmodern" (Lyotard), "post normal" (Funtowiz and Ravetz), "Mode 2" (Novotny, Gibbons, Evans??) or "reflexive modern" (Beck). Hence, the therapeutic revolution took place at the height of first modernity whereas the genome has been a product, or, stronger, a contributing force in the promotion of reflexive modernity. How do we recognise this?

First, consider the general contexts of the two "revolutions". The antibody entered into clinical practice as the first standardised product available on a world-wide scale. It radically changed the role of the clinician and the general practician through equipping him with a techno-medical object that actually cured people (indeed, it was only after the therapeutic revolutions that *hospitals*, as the huge institutions we know today, were established). Other highly important discoveries followed shortly after, significantly that of penicillin but also surgery. As implied by Ackerknecht, the effect was enormous, and it went smoothly along with a number of other developments taking place at the time: the medical profession became a corner-stone of the growing nation states, as exemplified through Robert Koch's close connections to the centralised Prussian government, military service and the sanitary movement. Health insurance schemes, social medicine and national health programs: all these things and more entered most western countries in the years between 1900 and 1930, taking the shape of a renewed social contract:

"The twentieth-century ship of state thus took health on board, paying lip service to medical thinkers and social scientists who taught that a healthy population required a new compact between the state, society and medicine: unless medicine were in some measure 'nationalized', society was doomed to be sick and dysfunctional" (Porter 1997:632).

Coming to the 1970s and 1980s, however, the picture has changed immensely. By now, the medical system has grown so big that the citizen patient is in need of legal protection *against* the powers of experimentalists and pharmaceutical companies, and even against the authority of the doctor himself (Rothman 1991). It also enters in a time in which feelings towards technological progress has grown ambivalent, the expert-lay divide has become problematic,

and in which the rationalisation of society has come to constitute a problem for itself (Beck, Holzer et al. 2001).

Genomics, then, considered as an attempt to recast clinical practice and the taxonomy of disease according to strict scientific principles, enters into a tougher social climate. Whereas immunology to a huge extent entailed a rationalisation of a society that was still guided by a strong sense of tradition, at least when it came to medical practice, genomics aims for the "rationalisation of rationalisation" (Beck 1998)[65].

In many ways, genomics is the direct heir to immunology: The attempt to recast clinical and experimental practice, thereby also the whole perception of disease, and thereby also society as such, through experimental activity. In first modernity and with the coming of the therapeutic revolution, a number of factors and actors had to come together: there was the building of the national state in which immunology and bacteriology entered into alliances with a number of other social actors and there was the close connection to a growing chemical industry, without which many of the discoveries made by people like Koch and Ehrlich could not have been made in the first place. Still, the different spheres of action could also co-exist in a relative separation and differentiation of work: Although the state supported its citizens with health insurance and instigated programmes of public health, the medical doctor remained the main "health politician" insofar as most decisions concerning the health of the individual patient were left at his discretion. This changed drastically in the late 1960s, and, as with so many other things in the late 20th century, the changes were first felt in the U.S:

> "Beginning in the mid-1960s, the practice of medicine in the United States underwent a most remarkable – and thoroughly controversial – transformation. Although the changes have altered almost every aspect of the relationship between doctor and patient – indeed between medicine and society – the essence can be succinctly summarized: the discretion that the profession once enjoyed has been increasingly circumscribed, with an almost bewildering number of parties and procedures participating in medical decision making" (Rothman 1991:1).

[65] When seen from this perspective, an irony appears: During the constant pronouncement of "revolutions" that took place in and around the HGP, the question may arise: who is about to rationalise whom? Proponents of genomic medicine warn clinicians that if they do not catch up with the latest developments, they will be left behind. At the same time, molecular geneticists are under pressure for not catching up with the latest "revolution" in informatics. Are they talking the same languages? Do they propose the same revolutionary rationalisations?

I will return to this part of the story in the later chapter on autonomy and patients rights. For now, the main theme is the muddling up of rationalities and disciplines that took place between first and second modernity. There were other, related and parallel developments as well: due to revelations of not-so-ethical research practices, not the least during world-war II, the state also started to take an interest in experimental activity. *Human rights,* as manifest in the Helsinki declaration, entered as a central consideration for policy-makers.

Then there are the issues of industry and the economy. As seen, medical research in the 1960s emerged as a main area of state investment, resulting in a radical growth of researches into basic physiology. The main (U.S.) actor in this process was the NIH. In the 1970s and 1980s, however, the economy changed and there was a general shift of focus towards applicable technologies intended to fuel a growing knowledge-based, global industry (Krimsky 1991; Wright 1994; Hughes 2001). We have seen how, in the 1980s, private capital came to make up a dominant part of research funding. A main worry of leading figures in the Human Genome Project, people like John Sulston, James Watson and Francis Collins, was, and remains, that private capital and restrictions upon exchange of information in the shape of intellectual property rights, will run off with the common goods.

Hence, there are *many* ways in which we can say that the genome enters into second-order processes of modernisation, rationalisations of rationalisation:

- The attempt to re-establish the scientific basis of physiology and pathology means a recasting of the medical knowledge-base. This recasting will be effected through the nexus of disciplines that make up the context of the genome
- the necessity of legal and political intervention
- the strong role of the economy and industry

All these factors were present also during the therapeutic revolution. The difference is that they no longer reside in the periphery, but threaten to take the centre stage. Hence, we get a "muddling up of rationalities" that question the old models of legitimacy:

"In dem Masse, in dem diese Gewissheitserosion der Rationalitätsgrundlage voranschreitet und anerkannt wird, kommen *alternative Wissensformen* ins Spiel, die möglicherweise immer schon latent Handlungen und Entscheidungen zugrunde lagen, aber als illegitim, weil unvereinbar mit dem jeweiligen Rationalitätsmodell angesehen wurden" (Beck and Bonss 2001:35).

Second modernity *is* this intensification of first modernity rationality and action, in the sense that the modern distribution of knowledge production and action organisation transgresses its own borders. This happens because each discipline and each action system has repercussions beyond its own domain of acting and knowing, and so the modern production of knowledge poses problems that cannot be solved within the old figures of thinking, speaking, acting and organising. In terms of classical sociology: Functional differentiation creates problems that cannot be solved within the model of functional differentiation (Beck and Holzer 2004). We may also state the point using expressions from Sheila Jasanoff (2004): In first modernity, the production of *scientific order* would generally coincide with establishment of *social order*. In second modernity, social order and scientific order may be found to be at odds with each other. Indeed, the reservation of part of the Human Genome Project's budget for research on legal, ethical and social issues is an expression of this fact.

The genome between system worlds and life-worlds

An overview of the situation cannot do without some understanding of that dimension in which the scientific object is thought to find its main application and legitimation: the life-world of the patient. As seen in the policy documents dealing with the prospects of a genomic medicine, a thorough re-education of the public as well as the medical profession is a necessity if technology transfer is to be a success. Genetic information is not much worth if there is nobody to interpret it and to translate it into the language of ordinary life, and for this to happen there must also be a rudimentary understanding of genetics in the population. For the moment, things may not be moving in the desired direction:

„Few medical schools adequately train their students to think mechanistically about disease; indeed the trend towards pattern-recognition medicine, away from basic science training, means that we are still far from educating the next generation of clinicians to apply the knowledge and tools bequated to us by the double helix" (Chakravarti and Little 2003).

And, according to Guttmacher and Collins, at the moment „confusion remains among health professionals and the public about the role of genetic information in medical practice" (Guttmacher and Collins 2002). But is it just a matter of giving „the right information" to people? In order for genetic information to become of value, it must also cross the barrier between two worlds (cultures): "It is evident that ordinary experience is almost entirely made up of secondary qualities. The fact that men of science have dwelt chiefly on something else,

something which ordinary men do not ordinarily consider, has separated them from their fellows" (Singer 1959:246).

The justification for establishing a scientific basis for the study of disease is obvious: the techno-medical object presents us with the potential for diagnosing, preventing and curing disease. It is easy to imagine how the antibody must have strengthened the power of the physician immensely: it put him in the position of administering prevention and cures with directly measurable effects. The position (expertise) of the experimenter as well as the clinician was made manifest through the object of the antibody. Due to the high specificity of the antibody with its antigen, direct intervention became possible. The causal mechanism described by that counterfactual organiser called *specificity* corresponded directly with the single diseases it was set to act upon. Hence, the specificity of antigen and antibody was capable of organising a wide spectre of actions: from experimenter to clinician to patient to public health official; and all of it was possible because it had an easily demonstrable effect in the life-world. Indeed, much information was not needed; the (techno-medical) object spoke for itself through its almost magical capacity for the organisation of action. And so it is also easy to imagine how it became a highly efficient vessel for the integration of social action on the level of the medical action system. As such, it offers a prime example of the organisation of action in first modernity: the gradual removing of the basis of decision-making from traditional knowledge through professionalized and standardised knowledge, by Tönnies named the transition from *Gemeinschaft* to *Gesellschaft* (Lash 1996).

The gene, on the other hand, is not (yet?) endowed with such blessed characteristics: its specificity is in most cases a dubitable phenomenon, insofar as it also relies upon interactions with other genes, with proteins, cell environment and so on. We have also seen that whereas the project of defining DNA structure may be unproblematic, the definition of the gene is a more complex affair (Fox Keller 2000; Carninci, Sandelin et al. 2006). Although there is a material basis to the concept of the gene, its value usually comes from its status as an immaterial object, *information*. Hence, in genetics, *communication* is essential to the proper administration of the object.

In addition to the epistemic uncertainties that may continue to haunt the gene, comes the fact that it is itself defined in terms of *future risks* to the patient's health, hence expressed in terms of probability rather than as certainty. This may seem a paradox: the advancement of

scientific certainty translates into uncertainty when communicated to the patient. This is particularly true with respect to multi-factorial diseases: the highest degree of certainty possibly attainable is by necessity expressed in terms of probability.

In addition to this comes the already mentioned *therapeutic gap*: the ability to pose diagnosis outpaces the ability to cure. This means that in most cases, the administration of the gene directly transposes the responsibility for disease from the medical action system to the individual patient.

These two features mark the gene as a prototypical object of second modernity: its character of being a *risk object* (Beck 1992) and its character of being a promoter of *individualisation* (Beck, Lash et al. 1996) of the responsibility for disease. In this context, the term "risk object" should be interpreted quite literally, insofar as genetic information about most diseases is transmitted, not in terms of certainty, but in terms of the probabilities that a certain state of affairs occurs in the future. Indeed, the goal of genomic medicine is to provide the patient with individually adapted genetic information, like the "$1000-genome" vision of Francis Collins. The information entailed is supposed to enhance the potential for therapeutic intervention through specifically manufactured and adapted drugs and changes of environmental influences that increase the risk of disease breaking out (Guttmacher and Collins 2002). For the gene to become an object on a par with the antibody, gene therapy or stem cell therapy have to become realities. So far they have failed to redeem the high expectancies invested in them.

Somehow ironically then, the attempt at establishing scientific certainty through exact diagnosis, may issue in the creation of ontological uncertainty (Giddens 1990) in the life-worlds. In order to prevent these effects we try to make sure that genetic diagnosis comes with proper counselling, either from a specially educated genetic counsellor or from a medical geneticist. This person finds him or herself as a mediator between two worlds, or cultures, that of the life-world of the patient and that of the world of exact knowledge, faced with the difficult task of integrating genetic information within the life of the patient. The gene crosses the border between two worlds, indeed also between two anthropologies, as described in the first chapter. The gene also has a different time and dynamic from that of the patient: the linear relation of genotype to phenotype is not the same as the circular time of the life-world (Heidegger 1962). I will return to these issues in more detail in the chapter on autonomy.

9. Patentability

I ask, what would a man value ten thousand or an hundred thousand acres of excellent land, ready cultivated and well stocked, too, with cattle, in the middle of the inland parts of America, where he had no hopes of commerce with the other parts of the world, to draw money to him by the sale of the product? It would not be worth the enclosing, and we should see him give up again to the wild common of Nature whatever was more than would supply the conveniences of life, to be had there for him and his family. Thus, in the beginning, all the world was America, and more so than that is now; for no such thing as money was any where known. Find out something that hath use and value of money amongst his neighbours, you shall see the same man will begin presently to enlarge his possessions

John Locke, *An Essay Concerning the True Original, Extent and End of Civil Government*

Patentability and intellectual property rights in general are continuations of the principle of the right to property as established by enlightenment thinkers such as John Locke and Immanuel Kant in the 17th and 18th centuries. According to Locke, man has the right to anything that is refined by him, to anything that he has worked with his own body and thereby removed from the state of nature. One oft-cited passage goes as follows:

"Though the earth and all inferior creatures be common to all men, yet every man has a *property* in his own *person*. This nobody has any right to but himself. The *labour* of his body and the *work* of his hands, we may say, is properly his. Whatsoever, then, he removes out of the state that nature hath provided and left it in, he hath mixed his labour with it, and joined to it something that is his own, and thereby makes it his property. It being by him removed from the common state nature placed it in, it hath by this labour something annexed to it that excludes the common right of other men" (Locke 1966:§27).

The right to property, Locke said, is not fundamental, but rather derivable from the right to life and the concept of labour. Through his labour, man acquires a right in the material object as shaped and refined by him. The primary role (and legitimacy) of the state, Locke stated, is to protect man's right to property. In the liberal tradition of thought, the contractual relation of right, property and state makes up central parts of the fundament. Due to man's right to his own body, he transposes this right onto the material world through working and refining it.

Intellectual property rights (IPR) constitutes a slightly different matter, insofar as they introduce the time-limited right to the techniques or methods by which nature is refined. Although itself not aq US invention, the strong propagation of intellectual property rights in the late 20th century has been a particular concern of that country's expansive industrial and foreign policies. It was first laid down in the U.S. constitution of 1787 in order to "promote the progress of science and useful arts by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries", quoted from (Krimsky 199:145).

As can be seen, the institute was intended as an incitement to *innovate*. This remains one of its main *Raisons d'Etres* and it is also the background of the most well-known economic theory about patents, the so-called *invention-inducement Theory*. Other theories tend towards emphasising the benefits of patents in promoting the *disclosure* of inventions (hence share information about new knowledge), the incitement they offer for investors to *develop and commercialise* inventions or their ordering function for the future *prospects* of an invention (Nelson 1997). No wonder, theories like these come very close to so-called economic theories of law, in which a law's general legitimacy and quality is assessed due to its ability to induce economic growth (Posner 1983). As long as the law remains within the closed-off boundaries of industrial regulation, such reasons may be adequate to most people. However, when these models intrude on other areas of law, such as constitutional law, public law or health law, many people will feel that as an illegitimate intrusion of the economy into areas were it does not belong. To cast the problem within a Habermasian language: When economic incentives come to set the premises also within these other areas, a debate about *substantial* rationales for legislation has been exchanged for technical or formal rational reasons. This is one good way of getting at the critical issues cast up by patentability and genetics: many scientists, bio-ethicists, lay persons, physicians and lawyers will argue vehemently against the intrusion of the economy into areas traditionally associated with the ethos of science, the medical oath and health care as a domain essentially belonging within the public sphere.

An intellectual property right is basically a contract between an individual, the inventor, and society. Patents are but one among a number of intellectual property rights; copyrights and trade secrets are others (Eisenberg 1997). In what follows, however, I concentrate on the intellectual property right of patentability, as that is the institute that has come do dominate the debate concerning regulation of bio- and gene technology. The main rationale behind the

contractual relation of patentability is as follows: By granting to the inventor the exclusive, time-limited rights to the economic and industrial profits of the invention, an incentive is offered for the creation of objects, designs, writings or techniques that may become of value to society at large. The transfer of surplus value to society, it is projected, takes place along two pathways: 1) through the public disclosure of the relevant information about the discovery, which is normally part of the patent application. There is a time lag between the filing of the application and the public announcement of the patent, granting the inventor the upper hand in the competition for its use; 2) after the patent has expired, usually after twenty years, the invention is in principle out in the open for everyone to use (Eisenberg 1997).

An important element in this process is that the *information* about the invention is made public, but not the monopoly on the use of the invention itself. Thus, the first "payoff" from the inventor to society comes in terms of (allegedly) useful information. Within traditional patent law, this non-restrictive sharing of information as opposed to the use of the actual object or material process has been a main rationale in the balancing of interests (Eisenberg 1997). As can be imagined from this premise as well as the previous sections, problems arise when the genetic object itself takes the shape of information.

Hence, I focus upon two problem complexes: one has to do with ethical and institutional concerns raised by the intrusion of industry and the economy into the general area of the life sciences; the other has to do with the institutional and regulatory problems arising from the attempt to apply traditional patent law to a fast-growing *information* economy. As before, the purpose is not to solve these questions in any detail, but rather to point to some general consequences that follow for the social organisation of action.

In what follows I go back in the history already told about the gene, but now we must try and see it from a different angle, namely that of patenting as a way of balancing the interests of actors from large-scale industry, small companies, the scientific community and the public at large.

Recombinant DNA technology

Patenting has been part of U.S. industrial politics since the making of the Constitution, contributing significantly to a number of techno-social transformations like the industrial, agricultural and the chemical revolutions (Krimsky 1991). For that reason, patenting had been

known to researchers within applied fields like engineering, agriculture and chemistry from the beginning of the 20th century. To most molecular biologists and biomedical researchers in the early 1970s, however, the phenomenon of patenting was wholly foreign to their daily practice, and insofar as it was made a subject it was generally condemned as opposed to the general spirit of those sciences (Hughes 2001).

There was a further legal reason for this: until the ruling in *Chakrabarty v. Diamond* in 1980, organisms or living matter were not considered patentable. This had been U.S. practice since a landmark ruling from 1889, in which the application for patent on a fibre growing in the needles of a pine tree had been rejected on the grounds that the composition of naturally occurring substances did not qualify as human inventions. "The commissioner's ruling formed the basis for what came to be known as the "product-of-nature" doctrine: that while processes devised to extract what is found in nature can be patented, objects discovered there cannot" (Kevles 1998). Hence, up until the 1970s and the coming of the new techniques of recombinant intervention, there would be little reason for life scientists even to consider the possibility of patenting. There were not many reasons for doing so: until the scientific and industrial syntheses of biological materials became a real possibility, scientific and legal imagination remained restricted to their respective domains of thought and action.

Patentability and the ethos of science

As described in the earlier section on recombinant DNA technology: although primarily involved in basic biomedical research, the main scientists in the field were well aware of the potential inherent in the new techniques, and news of the industrial and economic prospects also leaked to the media. Stanford University had set up an "Office of Technology Licensing" in 1970 to function at the interface between the academic and industrial worlds. Upon reading about the new molecular advancements, the administrator of the office, Niels Reimers, contacted Cohen and Boyer immediately. Cohen, although fully aware of the potential of the new technology, was surprised by the new prospects: "I suppose…that my framework was that one patents devices, not basic scientific methodologies", Cohen quoted in (Hughes 2001).

Cohen had other reservations as well, one of which is especially worth mentioning: the basis of the application was three papers on cloning produced during 1973 and 1974[66]. These were not the products of Cohen and Boyer alone: significant contributions were also made by

[66] See chapter on recombinant DNA.

Chang, Helling, Morrow and Goodman. In addition, the work built upon the work of Paul Berg's group that utilised the restriction enzymes developed by some other researchers, and so on. The point is: Whereas the papers that served as the basis for the patent application built upon the works of a whole community of researchers, only Cohen and Boyer were named as inventors of the new technology. The invention being as it was the outcome of a communal endeavour and not the sole achievement of two lone researchers, Cohen felt uncomfortable that the honours and rewards would befall him and Boyer only (Hughes 2001). Here then, was an early sign of problems to come: whereas science is basically a common enterprise, patent law favours the inventor, and ascribes to him not just the honours, but also the *rights* to the new product. This represented a decisive break with the traditional research ethos as described by Robert Merton, in which science is basically a communal enterprise based upon the open sharing of results and data (Merton 1973). Correspondingly, it also broke with the ways in which research had actually been carried out:

"For years we have sustained a flourishing biomedical research enterprise in which investigators have drawn heavily upon discoveries that their predecessors left in the public domain. Yet the nature of patents is that they restrict access to inventions to increase profits to patent holders" (Eisenberg 1997).

Technology transfer as property transfer [67]

Concomitant with the scant attention paid to patentability by life scientists was the role of patenting in American universities in general. As described by Sally Hughes, the attitude taken by most universities to patenting was passive: even though the technology existed within campus, its promotion in industry was not actively promoted. The technology was there for those who wanted to develop it commercially, but by most academic researchers commercialisation was generally regarded as a lucky by-product of basic research and not as a prime goal. Reimers saw this as an under-developed resource for university funding, and it was under these conditions that Cohen eventually came to accept the proposal: he and Boyer would stand as inventors and formal applicants, but the economic rewards as well as the patentability rights were to befall Stanford University and the University of California, where Boyer was working. Boyer, wanting to keep the royalties for him self, seemed not to be worried by such doubts. He did, however, have one reservation, namely that publicly funded research (NIH) was to result in private property rights. But as long as the patent was kept in the name of Stanford and the University of California, this was not a problem: a federal

[67] Technology transfer is "the process of converting scientific knowledge into useful products" (Office of Technology Assessment 1988).

agreement already allowed for transfer of ownership to inventions from the Department of Health, Education and Welfare to universities, and the NIH already held patent agreements with 65 universities (Kevles 1998). This may be seen as one early expression of the rising amounts of state incitements to universities to channel research into more applicable projects (Hughes 2001). But the universities may also be regarded as forerunners and promoters of what would soon be official U.S. patent policy. In 1974, Harvard University received a $23 million grant (over twelve years) from the Monsanto Chemical Company. The "donation" instigated what would soon come to be standard practice between industry and universities: universities received funding and property rights, industry receives exclusive license agreements on the resulting innovations (Kevles 1998).

One central argument legitimating such property transfers went as follows: under conditions of heightened interest from industry and commerce, the universities would be able to monitor the use and development of technological products through the possession of intellectual property rights. Concerning recombinant technology in particular it will be remembered that the handling of biohazard risks also had become a hot scientific and political topic at the time. Entering into the general climate that shaped the Asilomar conference, the proposal to commercialise a basic scientific technique did not go unheeded, and large parts of the scientific community reacted with dismay towards the developments. Hence, whereas significant parts of the community were considering the risks and potential adverse effects of recombinant DNA, others were lobbying its commercial and industrial application. To the proponents of each cause the potential political turmoil caused by the other must have been a nuisance: Berg and colleagues, responsible for the moratorium on recombinant DNA research were astounded by the political responses to their scientific whistle-blowing and eager to find quick solutions and to get on with research. In that environment, Reimer's intentions to further commercialise the technology even before it had been through a thorough risk assessment must have seemed contra-productive to the aims of many scientists. For Reimers, on the other hand, the political and public attention that came with the moratorium and the conference in Asilomar, was indeed bad news (Hughes 2001).

Following the Asilomar conference, NIH issued a set of guidelines for the contained use of recombinant DNA technology (briefly described in previous chapter). But as the guidelines applied to governmentally (NIH) funded research only, these could not be used to safeguard practicing scientists or the public against adverse effects arising through industrial research. It

would also be too far fetched to expect that the universities would take it upon themselves to regulate the industrial use of the technology. Thus it was that the traditional defence for universities possessing patent rights in order to control the technology disappeared down the slippery slope of economic development (*ibid*.).

Organising legal technicalities

In legal terms there are three main criteria for the granting of a patent: *Novelty*, to secure that the invention represents a genuine contribution to the present state of knowledge by adding something that did not exist before; *utility*, which is meant to distinguish the invention from basic knowledge; and *non-obviousness*, adding a qualitative dimension to the novelty clause. Minor advancements in existing knowledge may not count as genuine inventions (Eisenberg 1997). The Stanford and UCSF patent application on recombinant DNA obviously met with the criteria of novelty and non-obviousness. The utility of the procedures, however, required significant scientific and technological improvements (see previous chapter on recombinant DNA). Although the first application was filed in June 1974, the commercial utility of the technology was not properly demonstrated until 1977 with the successful expression of the hormone somatostatin. The political environment into which the application entered also contributed to the prolongation of the process of attaining the patent.

But the most significant problem came from a more profound source of uncertainty. In the original application from Stanford and UVSF, three patent claims had been raised on two principally different grounds. According to the U.S. patent statute, potential objects of patentability are defined as "any process, machine, manufacture, or composition of matter", quoted from (Eisenberg 2002). The original claims in the application had been for the *process* of recombinant cloning, but it had *also* been made to imply the actual *products* thereby produced, hence the specific "material composition" that would result from the use of the technology. How could one patent the actual products arising from the use of the technology?

In some cases, recombination techniques could be used to produce synthetic DNAs. This did not entail any specific problems, as it would offer up no issue that had not already been dealt with by the courts in cases involving the patenting of chemical compounds. A new chemical compound obviously constituted an invention; but what about hormones like interferon or insulin? How could you patent living things?

By 1976, Reimers learned that he would do better to withdraw the applications for product patents and to retain the process application only. Concerning the patenting of living organisms, the U.S. Patent Office awaited the decision of the courts concerning another case that had already caused a stir in the legal system. That other case, now famous for its statutory role in the commercialisation of biotechnology, was that of *Diamond v. Chakrabarty*.

Ananda Chakrabarty, working for General Electric, had filed an application for a patent on a bacterium constructed to break down oil spills. The bacterium was not a product of recombinant DNA technologies, but the principal problem of patenting living things was the same. At first, the Patent office Board of Appeals had rejected the claim to ownership put forward by Chakrabarty and General Electric on the basis of the precedent established by the "product-of-nature" doctrine. This decision, however, had been reversed by the Court of Customs and Patent Appeals. In the end, the case went to Supreme Court, which passed its final judgement in 1980. The question came to hinge upon the interpretation of the patent institute as established in the 35 U.S.C § 101, where it is stated that "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor", quoted from (Jasanoff 1995:256). Quoting a court decision from 1952, in which "anything under the sun that is made by man" had been made potential subject for patentability, the Supreme Court finally settled upon a radically expansive interpretation of the patentability statute.

In allowing for the patentability of living things, the decision (of 5 to 4 judges) was a signal to scientists and industry to go ahead with the establishment of mutual relations (Jasanoff 1995), 145. By so doing, the court affirmed and strengthened a general tendency in the regulation of the emerging recombinant technologies: from an initially sceptical attitude in the beginnings of the 1970s, to a shift of emphasis upon economic development and a down-grading of the original concerns about the inherent risks of the technology (Wright 1994; Jasanoff 1995; Kevles 1998; Hughes 2001).

This also reflected the concerns of many scientists: although many were eager to protect biology from industrial and economic forces, they were even more eager to get on with research. As already stated, the conference at Asilomar in 1975 had resulted in the issuing of a set of NIH guidelines, but these were restricted to publicly funded research only, and not to industry. But worries like these were alimented as many had come to the conclusion that the

initial uncertainties over the risks of recombinant DNA had been exaggerated. In that way, it was the court that came to set the order, acknowledging its duty to foster technological progress in accordance with the general political climate. Simultaneously, the court also took a passive stance by claiming itself to be powerless in the face of technological progress. Hence, says Sheila Jasanoff, an "apparent contradiction between opposition to and acceptance of a theory of autonomous technological development" was manifest in the courts judgement, but the tension remained unsolved (Jasanoff 1995:145).

There can be no mistaking the question of whose interest finally won out. At the time of the Supreme Court ruling, the case had gathered significant momentum, and strong groups were applying pressure to influence the decision. Among ten *amicus curiae* briefs that were filed, only one was in favour of the original rejection from the patent office, and that was the brief from the People's Business Comission (PBC) fronted by activist Jeremy Rifkin. The rest of the letters, all in support of the patent, came from actors such as Genentech, the Pharmaceutical Manufacturers Association, the American Patent Law Association, the New York Patent Law Association and the American Society for Microbiology (Kevles 1998). The actors may be let to speak for themselves:

In the *amicus* brief from Genentech, it was declared that revolutionary scientific developments were often controversial, and that it was not the business of the court "to attempt, like king Canute, to command the tide of technological development", quote from (Kevles 1998). Chief Justice Burger on his side, articulating the view of the majority, stated that "legislative or judicial fiat as to patentability will not deter the scientific mind from probing into the unknown any more than Canute could command the tides", quote from (Jasanoff 1995:144-145).

Clearly, Genentech and the Chief Justice spoke the same language.

Releasing the economy

Similar accommodations also took place along other pathways. During 1976 and 1977 the different issues concerning recombinant DNA were taken to higher levels of policy formation. After the application from Stanford, other universities followed, and so the problem was gaining in momentum. The director of NIH, the trustees of Stanford, and finally also Congress were eventually forced to decide on the complicated issues of commercialisation versus

potential biohazards. In 1978, the NIH came out as an outspoken supporter of the Cohen-Boyer patent.

The early recombinant debate arose in a time when public rights movements, environmentalists and other activists had succeeded in establishing a political agenda in which the adverse effects of new technologies loomed high (Wright 1986). As a consequence, in many states and on the federal level, politicians were considering strict security measures. In the state of California, a strict bill on regulation of all laboratories carrying out research on recombinant DNA was being planned (Hughes 2001). In 1976, senators Edward Kennedy and Jacob Javits made an appeal to president Ford to extend the NIH guidelines to industry as well, not just to publicly funded research (Jasanoff 1995). Tendencies like these caused a massive counter-campaign from scientists concerned that their research would be hampered by politics (Wright 1994). Berg and others who initially had been sceptical towards patenting now waged a strong pro-campaign for the general promotion of recombinant DNA technologies:

> "Berg, Cohen, Kornberg and others on campus, as well as scientists elsewhere, were mounting an active opposition. The lobbying effort, one of the largest ever waged over a technical issue before Congress, helped to persuade legislators that the scientific and commercial benefits of genetic engineering outweighed its potential risks" (Hughes 2001).

As the biohazard issue was mainly considered solved, scientists now came out as sceptical towards stricter regulation: restrictive rules on patentability and private interests would also come down hard on the scientific community itself, and research had to continue. This did not mean that the question of patentability had been settled within the community, but it meant that for the moment a lid was being put on the issue for the sake of the common good.

This also went well along with the general re-configuration of the economy under way, as well as university administrators' wish to utilize the commercial potential inherent in the new technologies. Scientists who wanted to reserve themselves against commercial influences ran the risk of losing out on the main developments in their field, as both state and private funding were flowing steadily in the direction of the latest technology. The permissive ruling of Supreme Court in *Diamond v. Chakrabarty* was an expression of this general tendency to adapt to the needs of science and technology.

Following the ruling in *Chakrabarty,* the Cohen/Boyer application was also granted. Thus, intellectual property rights had been established as a way of regulating research on living organisms. In the patent office, the Cohen-Boyer application and a stream of others that had awaited treatment could now be dealt with, and in December 1980 Cohen and Boyer's application was granted (Hughes 2001).

The Cohen-Boyer application had initially been broadly formulated: one patent for the process and two for the different protein products that would result (made by the use of respectively eukaryote and prokaryote DNA) (National Academy of Sciences 1997). What this implied was that the proprietors to the process and to the proteins would hold the rights to the essential tools and products of a whole new industry. The technology spread rapidly. Many smaller companies and research laboratories were already using the new technologies, now these had to pay a license fee to stay in business. The fees were not unreasonable, and were readily accepted by start-up firms and industry. The property holders found themselves in a unique position: the technology was easy in use and not expensive. Furthermore, it constituted the only available technology in the market and it was essential to further development. A *non-exclusive* patent was issued, meaning that anybody who paid the license fee would have the rights of use. This secured a wide dissemination of the technology. In contradistinction, an exclusive patent could have resulted in a situation of monopoly. Due to the wide-spread use even before the patent was issued, and because the technology was essential to anyone wanting to enter the business, there was little use in limiting the number of users. In 1995, the patents had earned its proprietors $139 000 000 in royalties (National Academy of Sciences 1997).

No doubt, patentability was not incremental to the new industry; development would have taken place also without legal intervention. But the institute did provide a first guarantee concerning the potential and viability of the new industry. In those early days little was known to outsiders about the true commercial potential of the field, and in that environment every patent granted to industry and research served as confirmation of the economic viability of the field (Hughes 2001). The main importance of the Cohen-Boyer patent, then, may not have been so much its direct stimulation of new research, as it was its capacity for organising and stabilising the new relations between industry, commerce and academy that were already taking shape: "The biotechnology boom that followed the widespread dissemination of recombinant DNA technology transformed the way universities manage intellectual property.

It also fundamentally changed the financial environment and culture of biological research" (National Academy of Sciences 1997).

For one set of actors, patentability was of prime importance. Those were the many small start-up companies that popped up at the interface of academia and larger multinational companies. As stated by the Organisation for Economic Co-operation and Development:

"Patents are especially important for biotechnology firms as many of them have no activity other than R&D and therefore do not directly exploit their inventions: they sell them, or the right to exploit them, to other firms. A legal property right is therefore needed for the seller to be protected" (Organisation for Economic Co-operation and Development 2003).

The main engineering companies to emerge in the late 1970s were Genentech, Genex, Cetus, and Biogen, the three first were American, the latter was a European company. Among the scientific advisors to these companies were many of the central persons from the early developments in recombinant DNA technology. Academic resources were soon absorbed in the market:

"In 1981, an investment company reportedly approached twenty researchers before it found one without a commercial tie. Since knowledge and experience were as critical to recombinant DNA ventures as capital, it was important to hire outstanding scientists before the supply disappeared" (Wright 1994:96).

The new companies would typically be situated in locations near to campus, where they could easily pick up information and personnel. One important quality measure of the start-ups became the number of PhDs connected to the companies (Wright 1994).

On the economic side, money came mainly from investment firms and venture capitalists. This meant that, in addition to personnel and economic resources, one of the most important assets of the start-ups would come in terms of rights to promising products. Holding patents became a means for negotiating one's way in the emerging market. In many cases, the sole capital of the start-ups consisted of the knowledge of academic scientists and the venture capital of their investors. In that landscape, property rights came to be of prime importance in negotiating the terrain. Research and development contracts would get short-time money, but holding rights to valuable substances meant a strong hand in the market, in attracting the attention of the big companies. The multinationals, on the other hand, used the smaller companies to probe the market before they entered into serious business. Only when the

recombinant DNA business was well under way, would the companies carry out their own research within recombinant DNA (Wright 1994).

But there was also the matter of a scarcity of natural resources and technical feasibility. As already mentioned, the main pharmaceutical and therapeutic aims of the new technologies centred on substances such as interferon, expected to be effective in the fight against virus and cancer, insulin for diabetes, as well as some other hormones (Wright 1986). The goal for the new start-up companies would be to achieve high-rate expression of substances like these. Next, when the technology and the rights were secured, they would contact one of the bigger pharmaceutical companies to discuss licensing or sale of the rights to the product. During 1979 and 1980 most genes for interferon were cloned. At the time, following in the wake of President Carter's "war on cancer", it was widely believed that interferon would provide an efficient cure for the disease. The rationale for this was another widely held belief, namely that cancer is caused by virus. Interferon had worked on virus (in chicken). Hence, it was inferred, it would also work on cancer. In spite of these dubitable presuppositions: due to frequent announcements of cloned genes in the media, the hype was kept up, and interferon became an early symbol of the new industry. It did not, however, produce the desired effects in the treatment of cancer (Rabinow 1996).

The first *commercial* product to emerge from the new constellations was that of human insulin, marketed by Genentech in cooperation with the pharmaceutical giant Eli Lilly in October 1982. This did indeed prove the value of the new technology, but it also proved the proverbial instance of the single swallow that does not make a whole summer. Although expectations had been raised high, -by media, scientists and investors alike, the commercial outcome of the radically increased investments in the field remained scarce. Equity investments in the genetic engineering companies rose sharply in the years from 1979 to 1982, but from then on the market cooled off (Wright 1994).

Emerging patterns

Regardless of what preceded what, the politics, the economy or the technology: it is hard to mistake the general trend of the early 1980s, when recombinant DNA technology became a major industry. It was a time of liberalising state control with the economy, in which science and technology came to be seen as resources for a new knowledge-based industry. In that situation, transfer of property rights from the public to the private sector was seen as one

important incentive for research, but also as a way of regulating developments. The state, it was argued in front of Congress, was not sufficiently aggressive in pursuing the commercial potentials offered by patenting regimes. Hence, property rights had to be transferred to the sites where invention and development actually took place. And if the universities were to deserve public money, they had to transform their production into commercially viable commodities, which could then be licensed or sold as intellectual property to private firms (Cook-Deegan 1994).

The *Bayh-Dole Act* of 1980, aimed to promote technology transfer through property transfer, was a paradigmatic outcome of this. In the years to come, the Reagan administration issued a number of acts to stabilise achievements and to provide incentives for coming developments: the Patent and Trademarks Amendments in 1980, the Trademark Clarification Act in 1984 as well as the Technology Transfer Act in 1986 (Cook-Deegan 1994). The amendments secured a gradual extension of the patentability institute: the Patent and Trademark Amendments were passed to secure small businesses and non-profit organisations receiving funding from government; the Trademark Clarification Act further removed restrictions on licensing, and by the Technology Transfer Act of 1986 many of the same rules were applied to large businesses. Federal agencies were also permitted to form consortia with private undertakings (Office of Technology Assessment 1988). The developments in biotechnology were paralleled by similar incentives directed at the more mature technologies of semi-conductors and computers. All these technologies were seen as essential to establishing the U.S. as a world market leader in the new knowledge-based economy (Doremus 1995).

Indeed, for those who endorsed the new politics, developments looked good:

> "In the mid-1980s, private funding for biomedical research and development surpassed NIH's; by the end of the decade, it was greater than federal funding from NIH and all other agencies combined. Catching hold of the best in new science became an important element in drug discovery, driving pharmaceutical firms to heavy research investments as a matter of financial survival" (Cook-Deegan 1994:307).

This also meant that the initial doubts concerning recombinant DNA had given way to the economic agenda of the day: the biohazard risk had been played down, and the scientific community adapted, some more willingly than others, to the newly established relations with commerce and industry. Concerning the question as to the patentability of living things, the ruling in *Chakrabarty* proved radical, and it lasted until 1988 until the patent office continued

to expand the policy of the court. This came with the so-called "onco-mouse" of Philip Leder (Harvard Med. School) and Timothy Stewart (Genentech Inc.), a transgenic mouse specifically engineered for the purposes of cancer research (Jasanoff 1995).

Patentability and sequencing

I will shortly turn to the question of the patentability of the human genome sequence. That is where many of the central issues of the recombinant DNA controversy are carried on most fervidly, and that is also where the story "ends". As in the recombinant DNA controversy, patentability claims were raised and continue to be raised, towards both the process and the product, the sequence itself. No doubt, as also seen in the case of *Chakrabarty*, the issue of the patentability of the actual product, a living organism, aroused most controversy. These problems were further sharpened when it came to the question of patenting human DNA sequences. Part of the problem arise because of the principal doubt about the patentability of (human) nature, by many perceived as the common property of humankind, and not something to be sold at the market.

But a significant part of the problem with DNA sequencing also arise because of the problems with applying traditional patent law to a product that has in the meantime turned immaterial: information. I will work my way into that problem-field by starting out with the patenting of technologies rather than the product. Hence, I focus briefly on some central "research tools" before I turn to the question of the sequence itself.

Research tools: PCR and DNA sequencers

It has already been mentioned how sequencing technologies were developed as a cooperation between a private company, Applied Biosystems, and a university, Caltech. Relating to patentability, here was an area of research that was actually accepted within existing practices, although residing in the periphery of the life sciences: patents were usually issued on tools, not on basic processes. That being said, it was not common for a research group to focus almost entirely on the development of new instruments; new techniques or technologies usually came about as by-products of research, or they were developed by instrumentation firms and companies (Hughes 2001). Leroy Hood at Caltech was one that spotted the direction of developments at an early stage. As part of the team that created the first protein sequencer in the late 1960s, he had continued to devote his work to the automation of experimental work. Under his lead, a group from Caltech consisting of engineers, biochemists

and molecular biologists, emerged as top in the field in instrumentation work. He was also the leader of one of the world's largest biology research groups, working at the forefront of molecular immunology (Cook-Deegan 1994).

DNA Sequencers. In the wake of the recombinant DNA industry, Hood's group at Caltech evoked further interest in the field by sequencing the genes of the new products, like growth hormones and interferons. Many scientists became interested in the new sequencers and synthesizers developed in the cooperation between Caltech and by Applied Biosystems (ABI). At the time, Applied Biosystems had been among the few actors within the market to believe in Hood's ideas, and so funding had been obtained on the premise of exclusive licensing to the company. Following the wide-spread marketing of automated sequencers at the end of the 1980s, the technology has become incremental to research in molecular biology and to large-scale sequencing, and at the time it gave a substantial push to the undertaking of isolating single genes. Although Applied Biosystems obtained the license from Caltech on condition of its sublicensing the technology on "reasonable terms", after the marketing of the sequencers critics have contended that the sub-licensing practices of ABI has been anything but "reasonable". Of course, ABI counters by claiming it's right to a "reasonable return" on its investments (National Academy of Sciences 1997).

Applied Biosystems has since become the world leader in synthesising and sequencing technologies, but they are not the exclusive holders to the rights of the technology. Other similar technologies were developed by other firms. In Europe and Japan, sequencing technologies developed along with research efforts. One other central actor in the field of large-scale sequencing machines has been the Swedish Company Pharmacia, founded in 1989 (Cook-Deegan 1994). Other, smaller companies have filled niches in the market, for instance by focusing on smaller-scale technology for use in ordinary laboratories. For these smaller companies, the institute of intellectual property rights is incremental to their survival in the market:

"DNA sequencing is more than just an instrument, it is a system. To make a viable product, all the disparate pieces need to be integrated. That makes for a challenging intellectual property and licensing exercise, unless you have the internal funds to do everything. You require instrumentation, software, chemistry and microbiology", Harry Ostermann, director of molecular biology at LI-COR, a small instrumentation company, quoted from (National Academy of Sciences 1997).

Again: although it is hard to say what the market would look like without the introduction of intellectual property rights, there is no doubt concerning it's centrality as a means for manoeuvring the terrain of the late modern knowledge economy. The landscape looks different to different actors, and as a consequence it may be hard to generalise the workings of intellectual property rights into any fully embracing theory, be it economic or otherwise (Nelson 1997), or into a total politics of technological and industrial development (Doremus 1995). In many cases, for instance, the incitement towards inventors working within smaller, start-up businesses is conceived of as being at odds with the interests of the larger companies, supposed to put the products into large-scale production and market them over a broad scale. This is so because the intellectual rights required by inventors, which are usually formulated in terms of very broad claims on any product that might follow from the invention, may render the final product caught up in a web of intellectual property rights and licences that makes it too expensive for it to survive in the market. In other words: "upstream" incentives for invention hinders "downstream" development of industrial products, a mechanism described as a "Tragedy of the Anticommons" by Michael Heller and Rebecca Eisenberg (Heller and Eisenberg 1998).

In the case of sequencing technologies, however, the working group on Intellectual Property Rights and Research Tools in Molecular Biology put down by the National Academy of Sciences, concluded that intellectual property policies had turned out for the better to everyone:

> "One might argue that patent protection served both the large company (ABI) and the small company (LI-COR) in bringing their sequencing technology to the market. In the case of ABI, patent protection afforded them the opportunity to develop a complex system of technology in an orderly and efficient manner…In the case of LI-COR, patent protection of sequencing systems enabled it to negotiate the cross-licensing needed to develop its product fully. In both cases, private support has driven the development and dissemination of a research tool. The public and private sector seem to have gained equally" (National Academy of Sciences 1997).

PCR. As mentioned above, the Cetus Corporation was one of the first start-up engineering firms to appear following the introduction of recombinant DNA. Only six months after Genentech registered on Wall Street as the first genetic engineering firm, Cetus followed its example, hitting the market in March 1981 (Wright 1994). The main target of the company up to that time had been interferon, but now most of the interferon genes had been cloned, and

prospects had to be sought elsewhere. They settled on another potential anti-cancer agent, interleukin 2.

But by the end of the 1980s, the company was on the verge of bankruptcy, and the main tactic of pursuing interleukin seemed an increasing failure. Although this may have been just as much a consequence of miss-management, interleukin also failed to come through in clinical trials (Rabinow 1996). But at the same time, another product was emerging as a more promising possibility, namely PCR. Although Cetus had approached larger companies like Kodak and Du Pont, this had been done with the main purpose of promoting interleukin, thereafter to use some of the money from that for more research on PCR. After some failed negotiations, Cetus finally achieved a partnership with the pharmaceutical giant Hoffmann La-Roche. Roche's prime interest, however, was not in interleukin, but rather in PCR, of which rumours were already circulating. In return for a contract on PCR, Roche would finance research at Cetus as well as give exclusive rights to the company on interleukin. This had been a problem for Cetus, as a Japanese company had already purchased the original patent rights for that substance. Roche, however, had purchased the rights from the Japanese company, and now could use it as a means of trade (Rabinow 1996). In 1991, the patent for PCR was sold to Roche for $300 millions. Although initially conceived as a diagnostic tool, PCR soon proved its usefulness in a wide variety of technologies. Significantly: In addition to creating the possibility to analyse genes from biological samples, it soon emerged as an essential tool for large-scale sequencing (National Academy of Sciences 1997).

Compared to recombinant DNA, there was the similarity of the PCR technology being essential to a whole new branch of research, if not a whole industry. Those who wanted in on the business had to purchase PCR. However, there were important differences as well: whereas recombinant DNA had not been intended for commercial purposes, PCR had. This was also reflected in the licensing practices of Roche. Their prime target was not to license the technology, but to sell products using that technology. For research purposes, lower licensing fees were offered than for purely commercial applications, and for diagnostic purposes, the fees were even lower (National Academy of Sciences 1997). Still, many researchers complained about unreasonable prices, the main problem being the price on the enzyme *TAQ polymerase*. For instance, small companies would complain about being shut out from both the market and from science due to the price on the enzyme (National Academy of Sciences 1997).

Sequences of nature, sequences of information

When the genome project was being planned, all of the above developments were reflected in the planning work. The report from the National Research Council, made by scientists mainly, restricted itself to the brief recommendation that "human genome sequences should be a public trust and therefore should not be subject to copyright" (National Research Council 1988), 100. The report from the Congressional Office of Technology Assessment, however, devoted a whole chapter to the issue of patentability and intellectual property rights. As remarked by one observer: "Because OTA performed assessments at the request of Congress, it generally avoided making recommendations in its report" (Walters 1998). In spite of this, maybe because of the closeness to political circles, the drive towards commercialisation of science was underlying the whole chapter: "Policymakers are shifting their attention to technology transfer as products derived from molecular genetics find their way to the marketplace, international trade imbalances worsen, and rising deficits intensify scrutiny of Federal budgets" (Office of Technology Assessment 1988). One explanation of the scarce attention to the subject offered by the NRC report could be that it was put together by scientists, not politicians, and that the views would differ between the groups:

> "Scientists fear that corporate participation will inhibit the free flow of information and impede scientific progress. Policymakers want to ensure that a large Federal investment in genome projects is translated into new products and services, ultimately creating new jobs and other economic benefits" (Office of Technology Assessment 1988).

Perhaps no wonder, then, that clinical benefit was seen as equal to the commercialisation of genetic tests and therapies *(ibid.*), or that patentability as a tool for technology transfer was principally regarded as a win – win situation: "Legal protections balance the social good stemming from wide disclosure of new knowledge against individuals' or companies' rights to gain from what would not have existed without their effort" (*ibid.*).

Hence, in spite of the descriptive and neutral tone alluded to by Walters (above quote), the report contained strong prescriptions for the policy of genome centres: "filing patent applications early and publishing data soon thereafter are optimal for encouraging rapid dissemination of knowledge, protecting inventors' rights, and preserving economic benefits in the United States" (*ibid.*). Patenting would ensure the public use of new information at the same time as the "inventors" (not "scientists") would retain their control with the product.

Because the patents would be granted in the U.S. first, they would also promote the U.S. economy by producing new products and services.

Non-patenting, however, was a possibility not to be encouraged. "Investigators may decide not to apply for a patent because they wish to avoid substantial legal costs and bureaucratic entanglements or because they believe that science should not become commercially oriented" (*ibid*.). Many arguments were served against such a policy on the hands of the genome centres: it would inhibit the full exploitation of an invention; the inventor would lose control with the product; it would be detrimental to commercialisation because the invention could be used freely by all, and it would invite exploitation of U.S. taxpayers' money from foreign companies. In impeccable American logic, the cases of penicillin and monoclonal antibodies were used as examples of inventions that had been exploited by a foreign nation: "In both cases, the United Kingdom claimed the Nobel Prize, but the United States reaped most of the profits" (*ibid*.). Finally, non-patenting was against federal intent, as recipients of public funds were required to report patentable inventions.

A number of concrete proposals were put forwards in order to implement patenting in an optimal manner:

- First, due to the stark increase in patent applications in biotechnology a considerable backlog at the patent office (PTO) had arisen. This problem was not peculiar to the genome projects, but as they would have to await treatment along with other biotech applicants, an upgrading of resources at the patent office was recommended (Office of Technology Assessment 1988). Already that same year, a new unit was created for the handling of biotech patent applications. In spite of the upgrading, the backlog continued to grow and companies and universities continued to complain about obstacles created by the regulatory bodies (Cook-Deegan 1994).

-A coordination of patenting policies at the main agencies was recommended, as no such thing existed at the time:

"At present, written material on patent policies at NIH, DOE, and NSF is difficult to obtain, and there is no single source of information on patent policies at all agencies involved in genome projects…The interagency nature of genome projects means that recipient institutions will often be funded by more than one agency. A clear presentation of patent guidelines at various agencies with explanations of early patent filing and the implications of doing so (and not doing so) might diminish confusion and promote commercial application" (Office of Technology Assessment 1988).

In this way *policy-goals* were clear: they followed the general direction of the Bayh Dole Act and the line of new legislation that followed in its trace. The question of *what* should be patentable, however, would prove much more difficult, and it would continue to haunt the genome projects until their end and beyond. In more recent times, evidence has been gathered to show that the complexity of the problem has backfired on the regulatory bodies meant to effectuate patent policy, as well as on basic medical research and its clinical application (Merz 1999; Paradise 2005). On such accounts, central policy goals may even be described as being at odds with the prescribed means for achieving those goals. I will return to this topic.

The OTA report, for all of the space devoted to the question of patentability, was less prescriptive than the short statement from the NRC report, in which the human genome sequences were simply declared public property. One obvious reason for this being so, was that this was also very much a legal matter, not for Congress to decide upon. It was a question for the courts and for case law to determine the scope of legal protection. Up until that point, there was no case law upon which to draw, and so the question had to be kept open. This was not least due to the novel character of the field, and the fast pace with which technology changed: "The principles for determining patentability do not depend on any particular type of technology, but interpretation of them does" (Office of Technology Assessment 1988). In general, the report assumed that the main inventions to flow from genome projects would relate to technology development and research tools, not to the sequences themselves.

However, the possibility that researchers try and patent *whole gene sequences* could not be ignored: single genes had been patented for years, and in 1987 Walter Gilbert had caused a great stir in the research community when he announced his intention to start the Genome Corporation, and to copyright the resulting sequence information and to sell it to scientists and industry (Roberts 1987). The OTA report also made a reference to a 1982 article by Irving Kayton, in which it was argued that clones and sequences could be subjected to copyrighting[68]. Anyway, single genes that had been isolated and then cloned were incremental to the new biotech business, and had been patented for years. It was, therefore, recognised that

[68] The possibility that sequences be regarded as *trade secrets* was also considered in the OTA report. However, the industrial practice of trade secrets does not go very well with the scientific tradition of free and open sharing of data (Office of Technology Assessment 171). But the fact that both copyrights and trade secrets were considered as forms of regulating sequence information does say something about the uncertainty of the field.

there was a "grey area…between invention of new methods and the data that result from them", and that further research into the matter was required (Office of Technology Assessment 1988). For these reasons, it was recommended and expected that Congress kept a close eye on developments. Concrete legislature means, however, were made difficult by the fundamental uncertainty of the field:

> "Further study is needed to determine whether and how biotechnology demands special treatment as intellectual property before legislative reform will be in order. This suggests that patent policies might be high on the agenda for congressional oversight but low on the legislative calendar" (Office of Technology Assessment 1988).

Although made topic of numerous discussions in ethics and DNA sequencing conferences, the issue regarding the patentability of human DNA sequences remained unsolved. Legal opinion varied: Rebecca Eisenberg argued that sequences could be patented according to traditional doctrine, raising the demand that the sequence (or the gene) be "isolated and purified". Under the general conditions that "the claimed invention is the result of human intervention", and that "the DNA sequence is identical to a sequence that exists in nature", existing patenting practice should be sufficient to regulate future claims, quote from (Cook-Deegan 1994:310).

Others argued that traditional patent doctrine would not suffice. Traditional doctrine could not simply be extended because the nature of genetic research had changed with the coming of (large-scale) sequencing. Knowledge of a gene's sequence would yield no information about the overall *function* of that gene. The process of establishing whether a sequence was "identical to one that existed in nature", therefore, was by no means a straightforward matter. If such a principle was to be interpreted literally by the PTO, it could halt patenting and research indefinitely due to the problem of determining the specific function of the DNA sequence. As is well known, this is one of the main challenges for post-genomic research. Hence, DNA sequences constituted a problem for existing patent practices, which mainly extended to the *products* coded for by specific genes, for instance insulin. Closely connected, there was also the legal claim for inventions to be of *utility*. In the case of insulin, establishing utility was straightforward. In the case of a sequence with unknown function, claims to utility would by necessity hang in loose air. In the words of Cook-Deegan:

> "At the root of the uncertainty was the new scientific process of discovering DNA sequences before knowing their function. It seemed intuitively clear that sequences, like mountains, could only be discovered, not patented. Yet it was equally clear that patents already protected the isolation and

purification of genes and developments of protein products encoded by them" (Cook-Deegan 1994:311).

Expressed sequence tags (ESTs)

Although fervidly discussed, the above-mentioned problems did not surface in a policy-context until 1991, when NIH scientist Craig Venter announced that NIH had filed patent applications for DNA fragments ("ESTs") taken from human brain tissue. As earlier described, the ESTs were mostly extracted from previously existing cDNA libraries used in ordinary single-gene hunts or mapping projects. Although traces existed for establishing the functions of the sequenced genes, significantly maps of other species and existing human gene maps, the function of the genes filed for patenting was generally unknown.

During the gene hunts of the 1980s and early 1990s in which the genetic basis of potentially useful products such as insulin, growth hormones and interferon had been found, there had been no problems establishing biological function and possible use of the genes. By the time the gene had been isolated and purified, its function, i.e. the proteins for which it coded, would also be known Indeed, in many early gene hunts, the genes were isolated on the basis of known function only (Strachan 1999). This distinction between the gene as such and the product resulting from its isolation and purification, constituted the main rationale for ascribing patents on genes. Because the gene had been isolated and purified (separated from the chromosome and inserted in a new medium), the *in vitro* production of a new substance useful for some diagnostic, therapeutic or research purpose became possible. It was the effort of this refinement that constituted the intervention necessary for patentability (Eisenberg 2002) (Cook-Deegan 1994). Although deviating from pre *Chakrabarty* practice, strong analogies to cases involving patenting of chemical compounds existed (Eisenberg 2002).

In the case of ESTs, however, the main problem was that the function of the isolated genes could not be known at the time of their discovery. Technical developments thus outpaced the legal system by providing cases for which there was no precedence. "Clearly, gene sequences has been patented before; what is different in this case is that NIH researcher Craig Venter, who is identifying and sequencing nearly a thousand of the gene fragments a month, has no idea what the vast majority of them are" (Roberts 1991). However, as the granting of patent claims had been liberalised during the 1980s and 1990s, there was indeed a chance that the newly discovered genes be deemed to satisfy the criteria of novelty.

Concerning *non-obviousness* the matter became even harder to settle, among other reasons because Venter had not been the first to consider the procedure of concentrating on the protein coding regions only. Among others, Sydney Brenner had proposed it for the genome project in England. What was new about Venter's approach was the use of high-throughput technology to sequence the regions and the index system developed for the cataloguing of the data (Cook-Deegan 1994). Whereas this might get him some way with the *process* claims, it was more than uncertain if the sequences themselves constituted a significant improvement of the prior state of knowledge. As remarked by James Watson, a stark opponent of the patent application, the sequencing machines themselves could be "run by monkeys", quoted from (Cook-Deegan 1994:311).

Utility claims would also be particularly hard to satisfy, as the functions of the genes were not known. However, due to the liberalisation of patent criteria during the last decade, patent lawyer Reid Adler commented that: "there are a number of uses well short of biological function that [could] satisfy the law", quoted from (Roberts 1992a). The fact that the application was articulated in very broad terms further increased the uncertainty: the application was for both the genes, the sequences, the proteins expressed by the genes and for any antibody reacting against the proteins (Cook-Deegan 1994). The main fear, both among researchers and industrialists, was that if the application was granted, future development of products involving any of the patented genes, gene fragments or proteins would be restricted by the NIH monopoly. Or, if patent claims on sequences were to become standard, then patents could be issued to anybody in the possession of an automated sequencer. Thus, a situation could be imagined in which intricate networks of patent claims and fear of litigation would stifle rather than promote invention and development. Furthermore, the risk was imminent that the patent claims would "foster secrecy among scientists, destroy the essential - and fragile – relations on which the Genome Project depends, and hamstring the biotech industry" (Roberts 1992a). The patent application definitely was seen as a further move in the direction of privatised science, in which secrecy, not openness would be the rule (Thackray 1998).

The idea of patenting ESTs did not come from Venter, but from Reid Adler, the NIH director of technology transfer, who had learned about Venter's work through a patent counsellor at Genentech (Cook-Deegan 1994). Hence, the story begins in a similar fashion to that told

about the Cohen-Boyer patent. It also continued in a similar fashion in the sense of promoting wide-spread criticism from the scientific community. Both the American Society of Human Genetics and the International Human Genome Organisation filed complaints against the application. Opposition also came from other federal agencies, themselves bombarded with complaints, and from within the NIH itself. In a statement from the NIH's own Advisory Committee for human genome research, the application was condemned on strong grounds:

"We are unanimous in deploring the decision to seek such patents. The subcommittee is particularly concerned that the claims widely reported in the press extend far beyond the partial cDNAs themselves to include the genes from which they derive and the proteins they specify. We believe such claims are inappropriate and deleterious to science because they establish false end points for identifying genes and their function" (The Advisory Committee for Interagency Coordination of Human Genome Research 1992).

However, the committee did acknowledge the importance of having the issue cleared for future policy and research, and so it was added that

"…because such patent claims have already been submitted, we believe that it is in the public interest and in the interest of science to determine promptly whether such patent claims meet existing legal standards and whether such standards are appropriate to the present case" (*ibid*.).

And indeed, this was a rationale on which to proceed that was shared by many. There was an urgent need to clarify the matter for the sake of a mounting number of similar cases in the future: "Indeed, one of the few things on which people agree is that lingering uncertainty is bad for industry and bad for international relations" (Roberts 1991).

Reactions also varied in the business community: "Industry, too, is leery, said Richard Godown of the Industrial Biotechnology Association, though it believes that NIH had no choice but to file the applications" (Roberts 1992b). Typically, large pharmaceutical companies, although recognising the need for clarification, would be sceptically inclined towards broad patent claims on the hands of private researchers, start-up companies or universities. In terms of product development, the large companies were usually positioned well downstream of the initial research, gene discovery. Whereas discovering ESTs could be a relatively cheap and straightforward matter, it was (and remains) the actual research carried out in order to transform basic insights into commercial products that constituted the main challenge for research, hence also the most costly part of the technology transfer. Therefore, the Industrial Biotechnology Association (IBA), while approving of the patent application,

also recommended that it be placed within the public domain rather than licensed to some private actor. On the other hand, the Association of Biotechnology Companies (ABC), which consisted of mainly small firms, and also of patent law firms, recommended that the patents, if obtained, be licensed exclusively to one firm only (Cook-Deegan 1994).

As argued by both Reid Adler and Bernadine Healy, the NIH application was not to be regarded as a step in some aggressive commercial enterprise on the hands of the NIH itself. It was a pre-emptive strike to secure that the patents were being kept within NIH were they could be distributed to industry in concomitance with the general trends in science policy. Hence the patent application for the ESTs was explained as the agency's way of carrying out the policies of the 1986 Technology Transfer Act, and a socially responsible promotion of commercialisation: "NIH has a record of utilizing the patent system in a socially responsible way. When NIH moves into the patent arena, it is with the public good as a driving force and not because scientists want to get rich", Healy quoted from (Roberts 1991).

And, indeed, this argument had something going for it, in the sense that it seemed to confirm the general trends of politics, commerce and science since the early 1980s. One further factor to have spurred the politics of NIH, was rumours that the Medical Research Conuncil of England planned to keep its sequence data to itself (Roberts 1991). These rumours, however, were denied by the MRC (Roberts 1992a). Anyway: If the NIH did not move, it would only be a matter of short time until somebody else did: be it Craig Venter, England or Japan. Then the possibility of influencing further developments would be lost. In the opinion of Cook-Deegan:

> "NIH acted reasonably in filing the applications before a broad public debate, because there was simply no time to carry on such a debate. Moreover, if NIH had not filed the patent application, under the 1986 Technology Transfer Act, Venter himself could do so if NIH waived its rights" (Cook-Deegan 1994:334).

On the side of policy-makers and industry then, a sort of determinism seemed to reign: the issue of EST patents was a logical outcome of the policies commenced in the 1980s, and it was a logical outcome of the scientific and technological drive towards large-scale automated sequencing. No doubt, the strongest protests were voiced from within the scientific community, which did not seem to perceive the case as a logical development, but rather as a threat to their very way of working and sharing results. Here is part of a *Science* report from a

public meeting arranged by an interagency group set up to clear the matters between the different federal agencies involved:

> "One by one, representatives from the American Society of Human Genetics (ASHG), the American Institute of Biological Sciences, INSERM in Paris, the European Community, and others argued that if NIH is allowed to go ahead, it will start a patent stampede that will destroy international collaboration and hinder product development" (Roberts 1992b).

Even Craig Venter conceded that: "The patent system wasn't designed to give me and a small group of people ownership of half the genome" (Roberts 1992b). Which more or less returns us to the issue at hand: a hole in the legal system was opened up by technological developments, and a policy-response was urgently needed.

As will be remembered from an earlier chapter, the case eventually caused both Watson's and Venter's resignations from NIH. Criticism mounted as NIH, in the midst of the furore, filed a second application, adding 2375 gene fragments to the ones initially applied for, leaving the total number at 6869. According to estimates at the time, this amounted to approximately 5 % of all human genes (Roberts 1992a).

The issue between the NIH and the PTO was not "settled" until 1994, when NIHs new director, Harold Varmus, seemingly reversed the politics of Healey. On the grounds that patents on partial DNA sequences were "not in the best interest of the public or science", Varmus and NIH withdrew the application for the ESTs (Anderson 1994). But, as can be surmised: the withdrawal, although a relief to many scientists, did not really settle the matter, it was just passed on to other actors:

> "It will now be up to private companies to test the legal waters, but their dealings with the PTO are likely to be much more secretive. Indeed, if their patents are rejected, they may keep that information to themselves, on the assumption that acknowledging defeat could depress the price of their stock" (*ibid*.).

The EST debate set for a new stage in the patentability controversy, one that has continued to haunt both biomedical research and patent law. As many times remarked, the root of the problem was the underlying uncertainty concerning the biological function of the cDNAs. Eventually, this issued in a debate concerning the status of so-called "research tools". The term "research tool" was defined by an NIH working group as follows:

"We use the term "research tool" in its broadest sense to embrace the full range of resources that scientists use in the laboratory, while recognizing that from other perspectives the same resources may be viewed as "end products." For our purposes, the term may thus include cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools (such as PCR), methods, laboratory equipment and machines, databases and computer software" (National Institute of Health 1998).

Following this definition, disease genes may be regarded as both "end products" and "research tools". Or, in Rheinerger's terminology: as epistemic or as technical objects. The definition will depend on the context in which the gene is being used.

During the early days of the biotech industry, when patent law was first applied to the field, utility would be immediately known to reside in the *therapeutic effects* of the proteins made by the cloned genes. This was no longer so. Instead, the patenting of gene fragments or cDNAs now had to be justified on the basis of utility for research purposes; most genes patented could not any more be justified on the ground of being "diagnostic" or "therapeutic". However, due to continually and rapidly improving genome maps, the identification of disease genes had become an easy task, and by 1995 diagnostics came to outpace therapeutics in terms of justifying utility criteria (Cho and Mertz 1997). This entailed a new stage in the story of patentability, insofar as the tools for the development of future products came to be debated, and not just the "end products", the therapeutic or diagnostic products themselves. Concerns were raised that exclusive licensing agreements would stifle research by ascribing monopoly on important technology platforms (National Academy of Sciences 2006) to a limited set of actors only (National Academy of Sciences 1997). Again, it became a question of striking a balance between a complex set of actors: basic scientists, small start-up firms, clinicians, patent attorneys, government agencies and large companies of differing kinds.

Expanding patentability

As indicated in the previous section on ESTs, the problems provoked by new ways of finding genes not only sharpened the debate about patentability; it also split the field of actors in new ways and it provoked new alliances. This was primarily a result of the need for industry and invention to expand the scope of patentability as the science involved increased in complexity. As commerce found its way deeper into research and clinical practice, worries mounted that these practices stood to lose more than to gain from the new alliances (Merz 1999).

As earlier described, patent law by and large reflects the policies instigated in the 1980s to commercialise university and public research, *and*, correspondingly, to turn research in a more commercial direction: "patents offer an additional incentive for researchers to pursue projects that have commercial potential" (National Academy of Sciences 2006). The ability of industry and commercial agents to set the premises of research was not just a side-effect of the effort to commercialise science, it was also a specified goal for research policy, which thereby also took a step in the direction of American industrial policy and foreign policy (Doremus 1995). This entails that, as with the ESTs, the tendency from the 1990s and up until today has been towards an expanding interpretation of patentability criteria on disease genes (Eisenberg 2002; National Academy of Sciences 2006). On the one hand, this is seen as a threat to the work of many scientists. The issuing of the Bermuda principles in 1996 was one reaction to this (Sulston and Ferry 2002). At the same time: As the complexity of the science and technology increases, the latest expressions of which is the science of proteomics, the incitement towards including private capital in research grows even stronger. Private capital, in many cases, will not let itself engage if patent rights are not issued in return. These developments are of direct relevance also to the expansion of genomic medicine.

In the late 1970s and early 1980s gene hunters generally went after the genes coding for therapeutic proteins: interferon, insulin, growth hormones. Except from the barrier of patenting living things, these practices did not prove great obstacles to the legal mind: Analogies could be drawn from the chemical industry (Eisenberg 2002). Intellectual property rights were transferred, first to start-up companies and then to pharmaceutical companies, securing the first major industrial boom in the field. However, the number of commercially viable proteins was limited, and only a few companies made a profit (Wright 1994).

With the coming of more advanced sequencing technologies and maps the possibility arose of finding genes without going by the way of biological function ("positional cloning"). During this second stage the genes discovered would prove themselves as *diagnostic* objects rather than therapeutic objects. The utility-claim of patent law thus had to be satisfied by reference to diagnostic rather than therapeutic potential. Whereas diagnostic patents were the fifth most commonly issued patent type in the years between 1981 and 1994, by 1995 diagnostic patents had moved up as number one on the list (Merz 1999).

In one further abstraction away from concrete utility, disease gene patents would now be justified in terms of their potential use as *research tools*. Insofar as disease genes became tools for the development of therapeutic products, there would be a therapeutic side to the utility claim, but it was no longer straightforward in the manner of the early technology. As the therapeutic potential was not obvious, it would have to be negotiated in order to satisfy utility criteria. Hence, these developments caused considerably more unrest in the biomedical community:

> "Patents on these discoveries, although similar in form to patents on genes encoding therapeutic proteins, played a different and less familiar role in the biomedical community, setting the stage for conflict between people and institutions that had barely taken notice of the first generation of gene patents" (National Academy of Sciences 2006).

Although resistance had also been voiced in connection with the Cohen-Boyer patents, researchers and medical doctors now opposed patentability on the grounds that patents would interfere negatively with both research and clinical practice. On the side of researchers, the main fear was that the use of patented genes as research tools would constitute infringements of the patents, leading to liability for the researcher or the research institution (National Academy of Sciences 1997; Heller and Eisenberg 1998). On the side of clinicians, it was feared that tests would become out of reach due to exclusive license agreements, or even that the mere use of the knowledge of genes that had been patented would lead to infringement: "So-called disease gene patents claim the observation of an individual's genetic makeup at a disease-associated locus when done for the purpose of diagnosis. They cover all methods of "looking at" that locus when done for the purpose of diagnosis" (Merz 1999). On this account, the mere *use of knowledge* about a disease gene in order to make a diagnosis may constitute infringement of the patent. In that case, it would not any more be the gene as such that infringes on the patent, but the use of the gene as *information*.

During the period between 1995 and 2001, the number of patents on genes issued per year rose from about 200 to almost 900 (National Academy of Sciences 2006). The year 2001 constituted a threshold, as the PTO issued new guidelines signalling a stricter policy, mainly through the introduction of the utility-criteria of "specific, substantial and credible" (Duke L. & Tech. Rev. 2001; Eisenberg 2002).

With the coming of EST patents, the above tensions sharpened: "The most obvious value of ESTs was not the speculative value that particular gene fragments might have for therapeutic

or diagnostic uses, but the immediate value that collections of such fragments offered for use in gene discovery" (National Academy of Sciences 2006). Thus, gene patents took a further step in the direction of research tools and away from being end products. Thus, the danger of the "anti-commons" effect, where upstream incentives for gene discovery stifles downstream product development, increased (Heller and Eisenberg 1998). On the side of small companies and patent lawyers, expanding the scope of gene patents became incremental to business: "The more claims, the better. At the end of the day, they may be valuable as bargaining chips.", Lewis Gruber, chief executive of biotech company Hyseq, quoted from (Abate 1999). On the other hand was the scientists' worry that research gets tangled up in legal battles over patentability rights or that they were excluded from the use of important research tools. I give one example:

In 2000, the PTO issued a patent on a gene coding for the gene receptor CCR5 to Human Genome Sciences (HGS). The function of the receptor was clear: it binds proteins called "chemokines" to the surface of specific leukocytes. The patent was for both the gene, the cDNA used to find the gene and for the protein coded for by the gene. But the function of that particular protein was not known, however, and so the patent application described its chemical structure only[69]. In spite of this, a patent was granted.

The protein's function had been described, however, in 1996 by a group at NIH that had discerned the role of the receptor to be that of binding the HIV virus to the leukocyte's surface. Even though the actual research on the receptor had been carried out by the NIH group, the patent was issued to HGS. This illustrates the fear of many scientists: although the NIH group did all the hard work, HGS possess exclusive rights to HIV tests applying knowledge of the receptor coded for by CCR5 (Duke L. & Tech. Rev. 2001; National Academy of Sciences 2006).

What was more, ESTs are stored in huge databases and not in the traditional clone repositories, so-called "wet laboratories". Although the tangible cDNA fragments upon which the information is built may be of scant value, the ESTs are valuable tools (probes) for searching out other genes. This is a propensity that they share with a number of other information sources stored in computers, like haplotypes, SNPs, and proteomic information

[69] Indicative of another expansive trend in court decisions of the 1990s: *novelty* and *non-obviousness* were made dependent upon chemical structure rather than upon "the prior art", i.e., what would appear novel or non-obvious to a practitioner skilled in the art (National Academy of Sciences 2006).

(National Academy of Sciences 2006). This raises the question of whether the information itself can be patented. If that be the case, a long-standing principle of patent law is up for negotiation: under traditional patent law, the patent is issued exclusively to the inventor in return for his publication of the relevant information about the invention. Says Rebecca Eisenberg:

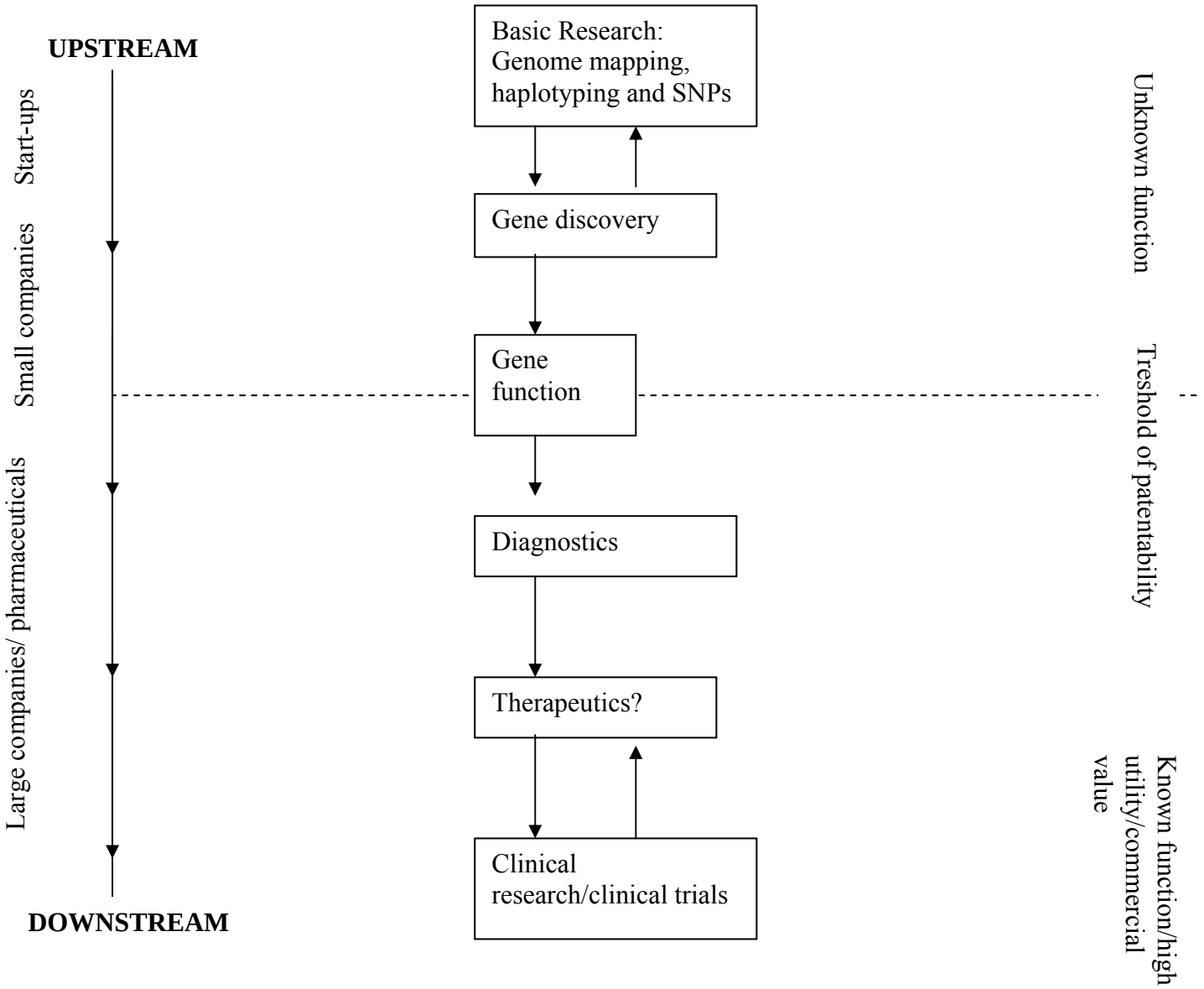
> "The distinction between tangible molecules and intangible information may do little work today in delineating the boundaries of patent eligibility in the face of recent decisions deemphasizing the importance of physical limitations in establishing the patentability of computer-implemented inventions. This shift in emphasis is particularly clear in *AT&T v. Excel Communications*, in which the court explicitly declined to focus on the "physical limitations inquiry" that had played a central role in distinguishing between un-patentable mathematical algorithms and patentable computer-implemented inventions in prior decisions. Instead, the court asked whether the mathematical algorithm is applied in a practical manner to produce a useful result…This approach appears to merge the issue of patent eligibility with the issue of utility, opening the door to patent claims to information so long as it is "useful"" (Eisenberg 2002).

As noted above, in 2001 the PTO issued new guidelines in an attempt at halting expanding patent practices. The restriction of patenting policy was meant to bring PTO practice into closer correspondence with recent court practice, especially the Federal Circuit's ruling in the case of *Regents of the University of California v. Eli Lilly and Co.,* where the court deemed the mere description of the method for isolating a gene or a DNA sequence to fall short of utility criteria. In short: the ruling constituted a move in the direction away from DNA fragments and genes as research tools, and in the direction of a practice in which molecular entities are first and foremost to be regarded as end products, in which physiological function has to be described in order to establish utility. Another reason behind the more conservative practice was the mounting criticism from the scientific community (National Academy of Sciences 2006).

However, in spite of tendencies like these the issue is far from settled. The new guidelines, requiring the utility of DNA material to be "specific, substantial and credible", may for the moment have sharpened the border between objects that are only valuable as tools for further research, and objects that are valuable for some more specific, practical application, such as therapy or diagnosis ("real world" utility). This does not mean, however, that the road to patenting ESTs is closed. What it means, however, is that applicants may have to sharpen the description given in the application in the direction of physiological function or some clinical potential (Duke L. & Tech. Rev. 2001; National Academy of Sciences 2006).

A hermeneutic of patentability

While running the risk of oversimplifying, we may display the dynamics of patenting disease genes as follows:



The figure is meant to display the balancing of interests among some central actors involved in patenting of disease genes. We may imagine two different ideological positions according to differing strictness of utility criteria:

1. *Liberal*.

Start-ups and small companies, having intellectual property rights and creative capital among their main assets, are typically interested in wide utility definitions in order to promote their survival in the market. In an important sense, these companies embody the ideal of innovation as a central driving force in the market. They are, according to Martin Kenney, what constitute the new biotech industry in the real sense of the word. They have made themselves particularly remarked in the United States, not the least because venture capital for many years remained a specific US phenomenon (Kenney 1998). Armoured with venture capital, they work closely with university scientists in order to create upstream innovations that can be patented and licensed to larger companies. However, in cases of too liberal patent policies, risks of "anti-commons" effects arise: "A proliferation of intellectual property rights upstream may be stifling life-saving innovations further downstream in the course of research and product development" (Heller and Eisenberg 1998). During the 1980s, when biological function was more easily foreseeable, the problem could be contained. In the aftermath of the NIH application for ESTs, private firms took over where NIH had left the business, and thousand of patent applications were filed. The increasing complexity of gene hunts led to a stronger opposition of interest in which the smaller companies sought patented research tools of yet unknown function (Duke L. & Tech. Rev. 2001). Typically, the space for the start-ups and the smaller companies will be wider in the early phases of a new technology when possibilities are still wide open. As the market settles, survival may get tougher: The true potential of the technology emerge and supply and demand enter a balance. This has been the case first with therapeutic proteins in the early 1980s, then with the genes responsible for the Mendelian disorders in the late 1980s and 1990s (National Academy of Sciences 2006).

2. *Conservative/social democratic*

In the more conservative alternative of patenting policy, upstream research is kept beyond patentability through stricter criteria of utility, novelty and obviousness. Although the patenting of therapeutic proteins in the 1970s and 1980s also were met with fierce opposition from the scientific community it was not until the more effective isolation of single genes in the late 1980s and early 1990s that the matter grew into a serious conflict. We might state that the debate expanded from a primarily moral debate over the patentability of living things and the ethos of science to a matter of institutional urgency:

"Patents on these discoveries, although similar in form to patents on genes encoding therapeutic proteins, played a different and less familiar role in the biomedical community, setting the stage for

conflict between people and institutions that had barely taken notice of the first generation of gene patents" (National Academy of Sciences 2006).

With the coming of the Human Genome Project and the EST debate, the conflicts intensified, and it came to accompany the project until its very end. After the fact, observers have noted that the Celera project was a commercial failure. In the words of Misha Angrist and Robert Cook-Deegan:

"Both the public and private sequencing efforts garnered their share of headlines, but Celera's genome-era business model failed miserably. In hindsight this is not surprising: Why would drug companies pay millions of dollars for sequence data that would be publicly available just months later? Within 18 months of the White House event [the joint declaration of the two finished projects], Venter was disposed as CEO of Celera, and the company refashioned itself as a drug discovery and development firm. The genome wars officially ended in April 2005, when Celera announced it would donate its sequence data to the public databases" (Angrist and Cook-Deegan 2006).

But this outcome was not obvious at the time. Had Venter succeeded in his undertaking to outpace the public project, and had not the Genome Project speeded up drastically so as to place the genome within the public domain before it could be patented by Celera and Human Genome Services, the story could have ended differently. For instance, it could have gone with the genome (at least the commercially interesting parts of it) as with the BRCA genes, responsible for hereditary breast and ovarian cancer:

The gene BRCA2 was discovered simultaneously in the United States, by Myriad Genetics, and in the United Kingdom, at the Institute for Cancer Research (ICR). Patents were issued in both countries in 1995. Myriad Genetics, which also possessed the IP in the related gene BRCA1, eventually won property rights over both genes in both the US and in Europe after long fought legal battles. The company immediately exercised its exclusive rights by threatening to sue any laboratory performing the tests based upon the BRCA genes. In the opinion of John Sulston:

"By claiming property rights to the diagnostic tests for the two BRCA genes and charging for the tests, Myriad is adding to total health-care costs. Even worse, once scientists really understand how the BRCA1 and 2 mutations cause tumours to grow, they might be able to devise new therapies. But because of its patents, Myriad has exclusive marketing rights. Throughout the formidable task of sequencing the human genome, we were faced with the question of research-related proprietary rights. Although the full impact of Myriad's aggressive approach was unclear in 1995, it was clear where a focus on commercial profit and patents would lead. What was needed was a commitment from the international sequencing community to make all genome information publicly available and not to parcel it out via individual deals between companies and researchers" (Sulston 2002).

However, in spite of talk of the genome being the common heritage of humankind, and of making it accessible for all, Sulston clearly realises that the genome in itself, far upstream of any practical application, is no good to humankind if not translated into therapeutic or diagnostic products. And so other actors inevitably enter the picture. Referring to the danger that ESTs be patented, Sulston recounts:

> "In 1994 a white knight had come along in the form of the pharmaceutical company Merck…The big companies weren't any happier than the academics that upstart genomics companies looked like cornering all the rights to valuable genome information. Merck funded a massive drive to generate ESTs and place them in the public databases, where they would be freely available for all (Sulston and Ferry 2002).

Of course, Merck was not doing charity work:

> "The company was worried about its freedom to operate in future years, since upstart companies like Human Genome Sciences and Incyte Genomics were filing patent applications on hundreds of thousands of snippets of genes. Such patents threatened to lock up exclusive rights to make, use, or sell the human genes of which the snippets were only a part, creating thousands of "toll booths" along the way to producing final products" (Angrist and Cook-Deegan 2006).

For all the competence in drug development and downstream research on the hands of the large companies, the best scientists tend to be drawn towards the universities (National Academy of Sciences 2006). And so the big companies will remain dependent on the universities and the smaller companies. With those prospects, it is little wonder that many upstream researchers, working with processes less likely to be of direct commercial value, and the large companies share the interest of keeping data resulting from basic research within the public domain.

Clearly, displaying the process from upstream research to downstream product development in the above schematic linear fashion proves too simple when it comes to the dynamic of patenting the genome. As indicated, many developments, technological, legal, economic, scientific and political go into defining the relations between the central actors involved, and the expansion of the field is accompanied by constant renegotiations between the actors. I have tried to display this dynamic through changes to the institute of patentability as an organising principle. As technological developments and political goals expand, so does the institute of patentability: from therapeutic proteins in the 1970s/1980s, to single genes in the 1980s/1990s, to the whole genome in the 1990s and into the 21st century. As the single technologies settle into more or less stabilised relations, technological development is already

on its way to the next stage (National Academy of Sciences 2006). From the perspective of the new technology, prospects are still out in the open, intense innovation is required, and so there is a push towards liberalising utility criteria. In this race, proponents of more conservative patent criteria, like many scientists and drug companies, are fighting to keep basic physiological knowledge in the public domain and to secure that anti-commons effects do not occur to the process of knowledge and product development. However, the shear speed of the process leaves regulatory bodies struggling:

"Although the same patent laws apply to all fields of technology, new technologies inevitably present USPTO and the courts with new problems in the interpretation and application of old standards to determine such issues as patent eligibility, utility, novelty, nonobviousness, and adequacy of disclosure. Because the resolution of legal disputes takes time, a lag between the emergence of new technologies and the resolution of disputed issues of patent law that the new technologies raise will occur. Most of the existing legal precedents involving genomic patents address technology that is at least a decade old. Important issues concerning the patentability of ESTs -a technology from the early 1990s – are only now being addressed by the Federal Circuit" (National Academy of Sciences 2006).

And, in the words of Rebecca Eisenberg:

"One might expect that the Patent and Trademark Office (PTO) and the courts would have resolved this issue [ESTs] many times over as the industry has pursued and litigated patent claims covering biotechnology products; one might also expect that biotechnology patent law would now be entering a relatively mature phase in which fundamental questions have been resolved and the issues that remain to be addressed are incremental and interstitial. Instead, the patent system is struggling to clarify the ground rules for patenting DNA sequences, while years worth of patent applications accumulate in the PTO. What accounts for this persistent lack of clarity about how patent law applies to this technology? A significant part of the problem lies in the shifting landscape of discovery in genetics and genomics research. The patent system, which, inevitably, requires time to resolve even routine matters, has so far focused primarily on the discoveries of the 1980s" (Eisenberg 2002).

Stephen Hilgartner, with a special regard to biotechnology, criticises intellectual property rights practices for not being up to the challenges of the late modern information economy. Being themselves central tools in promoting that economy, intellectual property rights were from the very inception incentives for *technical innovation*. Their primary technical character and narrow social and cultural scope leave intellectual property rights as particularly ill-suited tools for regulating the complex set of interests that the field has come to encompass:

"Beginning in the 1980s and 1990s, decisions about intellectual property became visible and contentious public issues. A variety of actors – including many NGOs, academics, scientists, industry groups, and governments – now view decisions about intellectual property not as rational outcomes of

autonomous processes of legal reasoning, governed by precedent and safely left to appropriate experts, but as political choices with profound stakes" (Hilgartner 2002).

Hilgartner therefore proposes that the innovation-centric perspective of intellectual property be replaced by a rights-based perspective that is capable of articulating the central concerns of all the actors involved. The narrow intellectual property perspective blinds us to the fact that new intellectual property actually infringes on the territory of other actors:

"The politics of intellectual property often involve conflicts between the new claims of IP holders and the established practices of other parties. In keeping with the notion of an endless scientific and technological frontier, innovation-centric theories treat IP as new property – truly novel holdings staked out at the leading edge of knowledge production. Because IP emerges at the frontier and conveys rights to previously unexplored territory, it cannot impinge on earlier rights. But the frontier metaphor should perhaps give us pause; for the history of colonialism shows that land that distant powers perceive as uninhabited is sometimes occupied by other people. If innovation-centric theories situate IP in an unpopulated landscape, a rights perspective positions it in a web of social relationships and practices. From the rights viewpoint, new IP does not simply fill a vacuum but is introduced into a field of social actors. Put otherwise, intellectual property not only conveys rights to virgin territory but also curtails existing rights and transforms social practices on the (already existing) ground" (Hilgartner 2002).

Being no stranger to the mapping metaphor (Hilgartner 2004), Hilgartner draws a picture of the landscape into which intellectual property is wading. No doubt, there is an imminent danger of technical legal and scientific problems coming to intrude upon the public territory, significantly that of public health care.

The two versions of patenting policies (ideologies) described above may both suffer the risk of contributing to this tendency, although the one more than the other. The *liberal* version basically seems to set innovation and commercialisation as equal to social benefit. The small start-up and biotech companies make up typical embodiments of this vision, but it is also to be found within many policy-documents of American public agencies. NIH has, since before the politics instigated by Carter in the late 1970s and continued by Reagan in the 1980s, been a promoter of innovation-based policies in the field of biotechnology. However, some of the problems with a too liberal policy seem to be dawning as the field expands to encompass more and more actors. The attempt to restrain patenting practice by issuing guidelines with narrower utility criteria in 2001 may be seen as one expression of this. However, this solution remains a technical, and not substantial one (Duke L. & Tech. Rev. 2001).

This leads us on to the more conservative version, which, in terms of known political ideologies may be aligned with a social democratic vision of patent policies. However, we see that the main worry within that vision also seems to focus on a rather narrow conceptual basis: First and foremost, it is a matter of securing that the genome remains within the public domain, accessible "to all". But, obviously, this remains a truth of a highly conditional value: The genome as such, printed out as pure information, amounts to something in the vicinity of 21 meters of book-lengths containing information that is incomprehensible to most. Even experts cannot understand it without recourse to heavy information technology and complex mathematical algorithms. Even when properly understood, the upstream information is a far cry away from most practical applications, and among "real world" applications *therapy* remains the most distant. Hence, also this version, although with a stronger emphasis upon the public good and health care, remains dependent upon heavy support from pharmaceutical industry and private investors if the potential of the genome is to be realised. Also this version remains dependent upon the articulations of the industrial-academic complex (Krimsky 2003), and as such finds itself within a somewhat expanded, but still linear vision of development and health care policy. The question remains open whether this policy-vision is capable of incorporating the sort of doubts concerning the "real-world" status of the genome described in the chapter on the clinical context. Is the information contained in the genome sufficient to offer a surplus of alternatives for diagnostic *and* therapeutic action? And if this vision prevails in the future negotiations on the interface of genomics and proteomics (translational research): what will be the costs of realising that potential? The genome project, and the effort to translate it into genomic medicine, naturally leads onto techno-scientific undertakings of even higher complexity and greater technical and economic demands: proteomics, haplotyping and individualised pharmacogenetics (Guttmacher and Collins 2003; National Academy of Sciences 2006). In this process, the intellectual property landscape will have to change again:

"Proteomics is far less advanced than the field of genomics because robust technologies to study the structure and prevalence of all proteins in a cell in a high-throughput manner are only now being fully developed. The challenge that proteomics faces is enormous because of the finding that many genes code for multiple proteins, and those proteins are modified post-translationally in complex ways" (National Academy of Sciences 2006).

Which should push developments in the direction of innovation and developments again: "As discoveries stemming from genomics/proteomics are transformed into valuable items of intellectual property owned by universities, the new generation of biologists will yield ever

more influence" (National Academy of Sciences 2006). These developments, it is professed, may prove even more drastic to the pharmaceutical industry:

"Until very recently the field of human genetics has been restricted to studying diseases whose etiology can be traced to mutations in a single gene (e.g. cystic fibrosis). However, few common diseases are monogenic…For statistical reasons, relatively large populations will need to be studied to define the relative contributions of each change in the DNA sequence or degree of methylation, mRNA expression level or protein concentration, and degree of post-translational modification. The opportunity to create intellectual property is rich, and it is possible that it will be difficult for one patent to block the development of these tests. For example, in gene expression arrays, many genes tend to show highly correlated expression levels; thus, it is often possible to substitute one gene for another without substantial loss of predictive power. Because of the need to conduct substantial clinical trials to prove the practical value of these polyanalytic tests, however, the companies that develop these tests will have proprietary products" (National Academy of Sciences 2006).

These may be speculations about future developments. However, research has already been carried out to investigate and assess the influence of intellectual property rights on research and on clinical practice (Merz 1999; Merz 2002; Cho, Illangasekare et al. 2003; Henry, Cho et al. 2003; National Academy of Sciences 2006).

During work on the 2006 report of the National academy of Sciences, investigating into the effects of patenting on research projects, sharing of research materials and clinical testing, it was found that:

- Intellectual property did *not* cause significant concern among practicing scientists, leading them to cancel or change the direction of research projects. This finding, however, had to be balanced against a general ignorance about patentability issues among researchers, and the results are expected to change as intellectual property comes to make up more of the everyday of scientists. Not surprisingly, a higher awareness of patentability issues was found among industrial researchers than among university scientists.
- The growing complexity of biomedical research is likely to cause greater problems with intellectual property, not the least due to the growing interdisciplinary character of the field, and because of the need to work in larger teams.
- Intellectual property seems to have a certain (negative) effect on the sharing of materials among laboratories. Also this tendency may be rising in the future.
- The decisively most significant effect, however, is to be found in the fields of clinical practice and diagnostic testing. Here, the results of the survey conducted by the NAS

corresponds to those found in (Merz 1999; Merz 2002; Cho, Illangasekare et al. 2003; Henry, Cho et al. 2003). For instance, in (Cho, Illangasekare et al. 2003) it was found that

"Twenty five percent of respondents [among test laboratories] reported that they had stopped performing a clinical genetic test because of a patent or license. Fifty-three percent of respondents reported not deciding to develop a new clinical genetic test because of a patent or license. In total, respondents were prevented from performing 12 genetic tests, and all of these tests were among those performed by a large number of laboratories".

And in (Merz 1999), it was concluded that:

"Monopolization of medical testing activities: (a) threatens to restrict research activities; (b) creates unacceptable conflicts of interest; (c) may reduce patient access to testing; (d) may lead to inequitable extensions of patent terms on tests and related discoveries; (e) grants to patent holders the ability to dictate the standard of care for testing, and to otherwise interfere with the practice of medicine"

Now, my main point in referring these results is this: The most immediate effects on the practice of research and medicine are *exactly* those that occur on the downstream side of research and innovation. In the future, the costs of applying the insights from genomics to health care in general must be expected to grow at even stronger rates than today. This is not the least so because of the growing urgency for genomic medicine to produce *therapeutic* remedies for the most common diseases:

"Prescription drug usage ultimately may be dictated by a given patient's genetic makeup. Instead of trying to develop therapeutics to relieve *symptoms*, drug companies will come under increasing pressure to tailor therapies to individual groups of patients sharing a particular genomic/proteomic signature or fingerprint (as well as certain nongenetic traits). This sea change will first become apparent in the design and execution of clinical trials, in which genetic predispositions to therapeutic benefits and risks will be analyzed…Such advances will, however, come with a price for pharmaceutical and biotechnology companies. The advent of personalized medicine may well bring an end to the era of so-called blockbuster drugs, because product development will be restricted to smaller target patient populations. To say the least, the current economics of drug discovery development, and marketing will change considerably" (National Academy of Sciences 2006).

If this be the case, the social democratic version of patent policies may not be far ahead of the liberalist vision in terms of articulating the social issues involved in an adequate manner.

We may now start to appreciate why it is that Francis Collins regards the issue of patentability as the main threat to his "$1000-genome" (Guttmacher and Collins 2003). We may also start to understand why he does not dream of an even cheaper genome: why not the $200 genome?

Personalised genomic medicine cannot be realised without substantial inputs from industry. Significant parts of the $1000-genome, therefore, are already reserved for the pharmaceutical companies, and Collins can only hope that the investments of these actors, in cooperation with the increasing complexity of the genome, will not consume all of his $1000 genome.

Let me try and relate to the analytical framework put forward in the earlier chapters. In chapter three I attempted to give a hermeneutic reconstruction of the experimental context and the negotiations with the material gradually leading to standardised objects, possibly also to powerful technologies. Recall also how, in the chapter on immunology, Paul Ehrlich managed to stay in charge of the manufacturing process, perform clinical trials, keep control with new products and with the ties to industry. But already at that early stage, ties were strained and it took a person in a very privileged position to keep some control and to retain the totality of the process within the positivist research ethos. Still, in general, the products were not exposed to industry until they had reached a sufficiently stabilised and purified form, until they had become technological objects. Not so with the second modern project of genomics. As seen in the exemplary case of ESTs, commercial ties have made their way well into the laboratory. ESTs may find themselves in the stages of the research process between epistemic and technical things in Rheinberger's sense when sought patented. The same will also be the case with other biological material, hence the discussion about the patenting of research tools. This is one outcome, adapted to the intersections of the experimental and the commercial, of the "rationalisation of rationalisation" taking place in second modernity.

10. Autonomy (we may all become patients)

There is no sense in being interested in
a child a group or in a society,
there is no sense if one cannot see in them before anything else,
the life it's capacity to founded upon itself
there is no sense in being interested in an ill person
or unwell a society if one cannot believe their readiness
and the capacity for proper recovery;

auto production organisation

Stereolab, *Spark Plug*

I now turn towards a description of the principle of autonomy as a central tool for regulating the relation of the patient to the growing health care sector. Central issues involved are research, basic and clinical, the diagnostic and therapeutic encounter, and the changes in decisionmaking that has taken place within medicine since the late 1960s.

These are broad developments, relating to a wide scope of issues in the health care sector and beyond: civil rights movements, ecological movements, consumers rights, and public rights are all somehow related to each other within the wider political landscapes of post-war political dynamics. For the sake of oversight I start by relating the issues to some of the previously described developments in the relationship between laboratory, clinic and the life-world of the patient.

Assembling the issues of technology regulation within the horizon of the clinical encounter…

Recall how we started out by considering the basic relationship between laboratory, clinic and life-world in first modernity. Following Claude Bernard we stated that it took the introduction of experimental action to establish the clinical encounter as specifically modern: the laboratory established the knowledge base for clinical interventions in the life-worlds. Thus, the laboratory so to speak inserted itself between the patient and the physician. As seen in the description of bacteriology and immunology, the program of experimental medicine was carried out with huge success by people like Louis Pasteur, Robert Koch and Paul Ehrlich. It has been noted how the organising principle of protein specificity by and large corresponded to the actions it was set to organise. This was not the least due to the basically therapeutic

character of the antibody, which proved itself instrumental in dispelling common diseases like tuberculosis and polio from western societies. Hence, we may state, the delegation of organisational powers to the techno-medical object was successfully carried out through the organising principle of protein specificity.

Moving into second modernity, our basic relation between experimental action, clinical application and the life-worlds of the patients has been complicated to a considerable degree. Let me start by considering the techno-medical object of the gene as constituted through the organiser of the central dogma.

The age of DNA research arose in the aftermath of the protein paradigm. Under the influence from that older principle, but also through the strong influx from the physical sciences and from strong programs of social engineering, the organiser of the central dogma was invested with the same specificity. The simple linearity of the DNA – protein relationship was invested with the same simplicity of causal mechanism as that of the foregoing antigen/antibody relation. However, in terms of technology transfer, the organiser of the gene, and later the genome, has not accomplished the same straightforward action-organising capabilities as its forerunner: more than fifty years have passed, and clinical applications are still modest. True, the discovery of single genes responsible for disease has been breathtaking. But so far discoveries have been restricted to that relatively minor subgroup called Mendelian diseases, and in terms of practical application that does not yet suffice to establish the gene as a globally organising principle of health care.

Hence the expansion to genomics, which has yielded the possibility of analysing the total set of interactions taking place between all the genes of the genome rather than analyzing them one by one and in isolation. In terms of causality, this shift of emphasis has been accompanied by a change from relatively simple gene – protein interactions to a much more complicated picture in which causality cannot be determined directly (as envisioned by Bernard) but has to be conceptualised in terms of complex systems theory, and issuing in results of statistical probability and risk. These developments further point towards the need for even more complex modes of analysis: mapping and relating haplotypes, SNPs, and proteomics.

Insofar as genomics have issued in concrete objects to be deployed in the clinical encounter, these have been of a diagnostic rather than a therapeutic character. A problem that has been

noted since the inception of the genome project, is that of the therapeutic gap, in which diagnostic ability outpaces therapeutic ability by far (Office of Technology Assessment 1988). In terms of the patient – physician relationship this state of affairs is problematic: The medical system, it seems, generates risks that it cannot itself fully remedy. Hence, so far, individualised medicine seems to issue primarily in terms of the *individualisation of risk* (Beck, Lash et al. 1996; May 2004)[70].

We have also seen that there exist *reasonable doubts* concerning the scientific and technological potential of the genome when transferred to the clinical context (Holtzman and Marteau 2000; Vineis, Schulte et al. 2001). Hence, if we allow for a stronger sense of scepticism, in which we also include scientific and epistemic doubts concerning the general status of the genome *qua* global principle, we may also forward a stronger argument: genomic medicine, at the pace with which it is moving, not only implies a transfer of *medical* risk. Insofar as the status of the genome is still a matter to be negotiated among a complex set of actors, the fast transition to genomic medicine may even entail a transfer of *epistemic and scientific uncertainty*: from basic research through clinical application to the particular patient. In that case, there is every reason to consider genomics not just a scientific experiment, but indeed a *social* experiment (Beck and May 2001). Elmore and Gigerenzer have shown how practicing clinicians already have problems in coming to terms with present-day risk diagnosis. This goes for understanding and interpreting the statistical findings as well as the actual communication of the findings in a comprehensible manner to the patient: "…most physicians are poorly equipped to discuss risk factors in a way that is readily comprehensible to their patients" (Elmore and Gigerenzer 2005).

Hence, both the genome, considered as a global organising principle, and the techno-medical objects that issue from it, contain uncertainties when seen from the perspective of the clinical encounter and from the perspective of patients. The smooth delegation of organisational powers that seemed to accompany the antibody has not yet materialised, and the promises of the genome remain, by and large, outstanding claims still to be cashed in. If this state of affairs continues to accompany the developments of genomic medicine, individual patients

[70] This statement should be read with some caution: whereas it is true that genomics, for the moment seems to transfer risk responsibility from the medical system to the patient, this is not to state that risk is individualised in every sense of the word. Genetic tests, especially for single gene traits, usually yield results that are distributed among the members of a family. But that aspect falls somehow outside the perspective of this analysis.

may even become the dumping ground of socially and scientifically produced risk responsibility.

This should not be taken to imply that genomics research is, *per se*, wrong or false; but it means that it is fraught with a number of uncertainty elements that need time to be sorted out. One problem, when considering the transfer of genomics research, is that it seems to have gotten itself entangled in a race in which the one thing that we do not have, is time: "For states, corporations, genomicists, technoscientific tools, and biomaterials alike, it has become a matter of survival of the fastest" (Fortun 1998). And, commenting upon the increasing speed of research in the genome project, Stephen Hilgartner writes that "a concerted effort to increase what came to be known in the genomics community as "throughput" was a- and arguably *the*- central theme of efforts to enhance genome technology" (Hilgartner 2004).

As seen in the case of patentability as a legal tool for regulating genomic research, this state of affairs may constitute something of a paradox: patentability was introduced in order to stimulate innovation and the commercialisation of publicly funded research. The success of that project, however, has resulted in regulatory problems due to the speed of developments. Legal institutions by their very nature move at a different pace than do technology.

If speed is a problem for the legal and political control with developments *qua* patentable product developments, which constitutes, after all, a narrow though important part of the social environment of genomic medicine, then we should expect the matter to be even more pressing when it comes to the complex clinic – life-world relations. This is so because the "technology transfer" to take place on that specific interface is subject to a much wider scope of social influences than is innovation for industrial purposes. Whereas the issues involved in industrial politics most certainly are complex, especially as they come to encompass a much wider set of influences and interests along with the growing number of actors involved, they still seem to be contained within the rather narrow scope of optimal product development.

In the case of the clinical encounter, however, the influx of a wider set of social and cultural interests cannot be ignored. Whereas the institute of patentability grew out of a relatively narrow legal practice designed to promote innovation for industry, the regulatory issues on the interface of the clinic and the life-worlds have grown out of very basic and general socio-political developments. Hence, the investigation into that problem complex will have to take

account of all of the hereto described developments as well as some that have only been briefly described in the chapters on methodology. The clinical/life-world interface, which can also be narrowed down to the somewhat simpler relation between physician and patient (Rothman 1991), has to be regarded in the light of very broad social dynamics.

However, before we turn to those broader developments, let us continue to consider the genome as an organising principle within second modernity, and the gene as a second modernity techno-medical object.

The problem can now be re-conceptualised as follows: there is a divide between the representation of the gene given us through the counterfactual principle of the unity of the genome and the actual accomplishments and consequences of the gene as applied to the clinical encounter. We have seen that there is no necessary relation between visions of genomic medicine and actual accomplishments, i.e. therapeutic outcome. In other words: social order does not follow automatically from scientific order (Jasanoff 2004). This is most clearly seen when contrasted to the organisational capacity of the antigen.

If it is correct that the search for scientific certainty has also issued in the creation of new uncertainties for the patient, this may also be a valid statement concerning the role of the physician. In short: the hunt for simple solutions in science, i.e. the attempt to establish genomic certainty at the bottom of physiological and pathological explanation, may issue in greater organisational complexity. This indeed seems to be the case with genomic medicine, as the effort to establish the "$1000 genome" gradually includes more and more actors from a wider range of scientific disciplines, lawyers and politicians as well as the industrial and commercial worlds. In the chapter on patentability, I referred to research indicating that the part of health care most negatively affected by intellectual property rights and claims so far has been exactly that of clinical applications of genetic and genomic technology (Merz 2002; Henry, Cho et al. 2003; National Academy of Sciences 2006). Where the utility of new products is higher, adversarial claims among the actors involved also seem to be rising.

In general, the notion often implied by politics of technology transfer, stating that the utility and commercial value of techno-medical objects equals clinical benefit, is dubitable. Research has been carried out that question such notions of technology transfer: Utility does not constitute an "endless frontier" along which new technologies and knowledge co-develop

smoothly with that of clinical benefit Schei & (Strand and Schei 2001). On the contrary, good reasons can be offered for the view that there are certain *marginal values* to the utility offered by new technologies. Fisher & Welsh (1999) found that, covering a broad range of medical cases (i.e. not just genetics), where medical interventions were intensified, a majority of the cases turned out adversarial to patient's health compared to cases where no further interventions were made (Fischer and Welch 1999; Strand and Schei 2001). And, having studied the utility of new medical technologies in the American health care system, Deyo and Patrick writes that

"Many medical advances offer real advantages over older tests and treatments. Others offer little, if any, advantage, and many have alarming side effects. Even the effective medical innovations are often oversold and overused…Economists and decision-makers agree that new treatments are a major reason for ever-rising health-care costs…these new treatments are a double-edged sword. Some of them are good, some are bad, and most are only partly understood when they become widely used. As doctors and manufacturers introduce medical advances, good money too often trumps good science. Vested interests, marketing, politics, and media hype often have more influence on how new medical advances get used than the best scientific evidence" (Deyo and Patrick 2005:5).

If we are to take these reservations about technology transfer seriously, we may become aware of a lack of institutions for assessing and regulating the un-intended long term effects of science and technology. Hence…

…it emerges that organisational problems increasingly reside between domains of action…

If these reservations about modern politics of technology transfer are valid, it is not primarily because of the science "itself" or because of the technology "itself". That would amount to a degree of determinism that cannot be sustained (Rheinberger 1997). It may very well be that the main problems, rather than reside with science and technology, or with "politics itself", reside somewhere in the spaces *between* these spheres of action.

By recourse to Ulrich Beck I have argued that the "rationalisation of rationalisation" entailed by the intrusion of law, politics and the economy into medical practice constitute problems of a specifically second modernity character:

For a long time, during first modernity, the above mentioned spheres of action would all reside within their own disciplinary and social domains. This is no longer so, one central characteristic of second modernity being that functional differentiation, the sharing of work,

becomes muddled up. The reasons behind these developments are complex and cannot be dealt with in a satisfactory manner here. Still, it does seem that the expansion of the economy as well as the expansion of technology throughout larger and larger segments of society has something to do with it. This does not return us to determinism: as seen, within the field of biotechnology, the accelerated developments in these fields were consequences of willed political interventions (in the 1960s, 1970s and 1980s), and not of science and technology actually being autonomous spheres proceeding uninterrupted by external force.

The rapid application of science and technology to new areas of life creates problems to the social order: domains of action, be they situated in the life-worlds (for instance pre-natal genetic diagnosis), or within the sciences and the professions, are interrupted by the attempts to re-establish the knowledge base for a new and more technically refined one. Let us take pre-natal genetic diagnosis as an example. For the coming mother, this diagnostic technology poses unprecedented choices. For instance, the question concerning abortion is not new, but the many factors that now enter into the basis of choice, are. Let's say there is a chance of the child being born with cystic fibrosis. Does this constitute a sufficient reason for abortion? Obviously, the doctor, on his side, faces a corresponding dilemma, insofar as the giving of medical and scientific advice comes to have such grave implications.

Regulatory bodies, by their very nature embedded within wide social structures, cannot work at the same pace as science and technology. This entails the risk that, even where satisfactory solutions seem to be found, we cannot assess the social good or bad of those decisions until years and years later. Because of the very speed of developments, technical rather than substantial solutions are sought. In matters genetic, where there is still no strong scientific consensus regarding clinical application, a widespread social understanding cannot be expected. In this context, the solution of giving to people (and doctors) the "proper information", as for instance argued by Guttmacher and Collins (2002), is hardly satisfactory.

The therapeutic gap of genomic medicine is one central example of these dynamics. In order to remedy the large gap between scientific and public understanding of genetic disease, we make sure that the genetic message comes across with proper information in terms of genetic counselling. No doubt, this is a necessary institution of the interface between genetics/genomics and society. But given the rapid advance of genomics into health care in general it is hardly satisfactory in light of the wider issues involved: (genetic) risk is

transposed from the medical action system, no longer capable of remedying the diagnosis, to the single patient. Following the therapeutic revolution (first modernity) the clinical encounter would be accompanied by some technology capable of ailing the condition of the patient. Now, the techno-medical object comes in terms of *information* rather than direct intervention, which leaves a surplus of alternatives for choice with the patient. In this situation, the legal and ethical institutes of *autonomy* and *informed consent* are called upon to regulate the situation: the patient is to be given full information about his or her condition, and he or she is expected to make a choice (autonomous) based upon that information.

From a legal perspective, it is particularly interesting how the attempt to legislate scientific research inevitably also issues in a "scientification" of the legal domain: in biomedical matters, there is no longer an independent ground for the law upon which to establish its premises. The legal decision now has to include scientific knowledge in its basis for decision-making (May 2004). In this sense, the legal and political agenda comes to be "determined" by that of scientific and technological developments.

Because there is no time or space (no other institutions are available), the situation comes to resemble that of Max Weber's iron cage of bureaucracy, in which only a limited set of technical solutions are available and wider questions of social value and consequence are excluded. One reason for this being so, says Beck, is that the categories in which we think are still characteristic of first modernity:

"Wir leben in einer anderen Welt als in der, in der wir denken. Wir leben in der Welt des *und*, denken in Kategorien des *entweder-oder*. Dies haben wir nicht etwa einer allgemeinen Begriffsstutzigkeit zu verdanken, nicht dem Versagen, sondern der westlichen Modernisierung im Stadium ihres Sieges. Die stinknormale Weiter–und–weiter-Modernisierung hat einen Kluft zwischen Begriff und Wirklichkeit aufgerissen, die deshalb so schwer aufzuzeigen, zu benennen ist, weil die Uhren in den zentralen Begriffen stillgestellt sind. Die "Moderne" (auch so ein Nebelwort, das die Sonne nicht aufgehen lässt) ist in ihrem fortgeschrittenen Stadium zur *terra incognita* geworden, zu einer zivilisatorischen Wildnis, die wir kennen und nicht kennen, nicht begreifen können, weil das monopolistischen Denkmodell der Moderne, ihr Industriegesellschaftliches, industriekapitalistisches Selbstverständnis, im Zuge der verselbstständigten Modernisierung hoffnungslos veraltet ist" (Beck 1993:61-62).

Applied to the context of the clinical encounter, this means that the concept of autonomy, while introduced into an organisational void as an answer to a real lack of intermediating institutions, is not capable of remedying the space opened up by genomic medicine: information still is no good remedy for a cure. One important reason for this dilemma, I take it, is the rapid pace with which new technologies are introduced. This may even lead us to ask

questions about the science "itself" or the technology "itself". However, from the very beginning, it has been argued that the scientific enterprise and the scientific object cannot be regarded in isolation from the wider social context of which they are part. Thus it is that they find themselves at the centre of a general social problem…

…which may be spelled out as a deterioration of trust in basic social institutions

By this, I do not mean that there is, as almost by necessity, *less* trust in second modern societies than in simple modern or traditional societies: "…those who see their world as a 'risk society' often find placing trust problematic; but it does not follow that they do not place trust, or even that they place no trust in those whom they claim to think untrustworthy" (O'Neill 2002:12). We are reminded of Wynne's conception of "virtual trust": often people may have no other option than to place their trust in a specific expert system (Wynne 1996). One central mark of second modernity is the phenomenon of *individualisation*, in which the individuals are set free from institutional structures established during first modernity (Beck and Bonss 2001). This, however, is not the result of personal choice *per se*, but rather an outcome of the *Strukturwandel* of second modern society (Beck and Bonss 2001).

What is meant, then, is that along with this change of societal structure (*Strukturwandel*), trust is also de-institutionalised. It is no longer caught up in state-governed institutions and mechanisms of interaction, but dispersed throughout society, to be found in local communities, civil organisations and movements or the like (Lash 1996). This may have both positive and negative consequences: increased possibilities of action and choice for those with the necessary resources (social, intellectual, cultural and economic), or participation in communities and organisations committed to the common good, such as NGOs, civil rights movements or charity. But individualisation may also issue in a "dumping" of social problems in the poorer segments of the population (Lash 1996). Or, were modernisation is actively resisted, individualisation may issue in "counter-modern" movements, typically instigated to re-establish some pre-modern social order, legitimised through reference to tradition (Beck 2002).

In second modernity, trust is redistributed, no-body knows exactly how, renegotiated and re-embedded within different configurations, be they primarily "public" or "private". For public institutions, this entails that their continued trust within the populations increasingly has to be

negotiated, be that in the face of new technological or moral challenges, organisational complexities, or claims to rationality that compete with the previous authority of the public expert.

"Where people perceive others as untrustworthy they may place their trust capriciously and anxiously, veering between trusting qualified doctors and trusting unregulated alternative practicioners, between trusting scientific claims and trusting those of greenish or counter-cultural campaigners, or modish therapies and diets, between trusting established technologies and medicines and trusting untested or exotic technologies and products. But they do not refuse to trust" (O'Neill 2002:12).

Let me finish this section by quoting from the summary of *Charter on Medical Professionalism*, issued by the European Federation of Internal Medicine, the American College of Physicians – American Society of Internal Medicine (ACP – ASIM) and the American Board of Internal Medicine in 2002. The point is merely to make clear that the problem of trust, as described in this chapter, not just exists in the heads of sociologists or social philosophers[71], but has moved to the center of attention also within the medical profession itself:

"The practice of medicine in the modern era is beset with unprecedented challenges in virtually all cultures and societies. These challenges center on increasing disparities among the legitimate needs of patients, the available resources to meet those needs, the increasing dependence on market forces to transform health care systems, and the temptation for physicians to forsake their traditional commitment to the primacy of patient's interests. To maintain the fidelity of medicine's social contract during this turbulent time, we believe that physicians must reaffirm their active dedication to principles of professionalism, which entails not only their personal commitment to the welfare of their patients but also collective efforts to improve the health care system for the welfare of society", *Charter on Medical Professionalism* (The Lancet 2002)

So far, this chapter has been heading steadily down the slippery slope: starting out with the clinical encounter and the technology transfer projected by proponents of genomics in medicine, we noted the fundamental uncertainty, epistemic, social and legal, of the technology transfer to take place. The genetic object comes in terms of information about future risk, and so places a heavy responsibility on the patient. We then noted that this is not just a matter of proper transfer of technology, but that we are dealing here with generalised problems of social institutions in second modernity, problems that have to do with legitimacy and of trust. A smooth technological solution seems not to be in sight, especially since future developments in genomics are likely to be partial, never global (Brenner 2002). As seen in the

[71] Although dealing with it almost all the time, the problem of trust as a distinct problem to be dealt with has received remarkably little attention from bioethicists (O'Neill 2002).

chapter on patentability, further sources of uncertainty are introduced as techno-medical innovations of high utility, -notably in therapeutics, are also the ones that are invested with the highest degrees of commercial interest.

Changes in the ways in which we trust in experts in general, and in medical doctors and the health care system especially, is a useful horizon, or backdrop, against which to contrast the clinical encounter. As noted by O'Neill, the patient – physician relationship may be regarded as the "prototype of all professional relationships", and as a "paradigm of a relationship of trust" (O'Neill 2002:17). However, as the question of trust is very broad, I return to the main line of argument of this project, namely that of action and choice in the context of the clinical encounter. I do so by turning to the history of bioethics as centred round the principles of autonomy and informed consent.

Autonomy

The concept of autonomy, or self-governance (Harris 1985), stems from liberal philosophers in the seventeenth and eighteenth centuries like Locke and Kant, and was originally invoked as a legal guarantee for the protection of the individual against the powers of the state. In the ethical and legal philosophies of Kant, in which the concept is articulated with the greatest clarity, the ethical concept of autonomy is of essential importance as a blueprint for the legal and political drawing of *boundaries* for the powers of the liberal state. These boundaries, on the side of the citizens, issue in terms of legal and political *rights* (Locke 1966; Kant 1968).

According to Locke, the „great teacher of the Enlightenment" (Taylor 1989), the rights and duties of the citizens have their wellspring in the social contract, entered upon by equal and rational men, all of whom possess a basic right to property in their own person: „Though the earth and all inferior creatures be common to all men, yet every man has a *property* in his own *person*. This nobody has any right to but himself" (Locke 1966). The state is presumed *consented* to through the social contract, in which citizens make the joint commitment of submitting to the rule of law. Through the social contract the state is invested with the power to regulate the interactions of men in order to escape from the state of nature, in which everybody is against everybody in a state of lawlessness. Hence, the citizens have a legal and ethical *duty* to submit to the rule of law in the interest of the common good. Nevertheless, the relationship of rights and duties go both ways: the single citizen is to be protected from undue encroachments from his fellow citizens and from the state itself, and this relation is conceived

of in terms of the *rights* of the citizen. Hence, autonomy works in two directions simultaneously: it ascribes rights and it ascribes duties.

If we turn to Kant, the rights perspective is grounded in the fundamental *worth* of the person:

„der Mensch, und überhaupt jedes vernünftige Wesen, existiert als Zweck an sich selbst, nicht bloss als Mittel zum beliebigen Gebrauche für diesen oder jenen Willen, sondern muss in allen seinen, sowohl auf sich selbst, als auch auf andere vernünftige Wesen gerichteten Handlungen jederzeit zugleich als Zweck betrachtet werden", (Kant 1968:BA 64-65).

In what follows, I will focus on the application of autonomy as an action-regulating principle when applied to the sphere of health care in general and genetic/genomic medicine in particular. Fundamentally, this means that I take a look at how the autonomy principle emerges as an essential tool for the negotiation of new relations between patient and physician in the face of new technologies, a fast-growing health care system and intrusions of the economy. Complex issues of disciplinary boundaries come together with the question of *trust*, which is itself situated on the borders between the medical system, other scientific disciplines or systems of action, and, last but not least, the life-world of the patient.

Autonomy as an organising principle for health care and research was not introduced until the late 1970s, following which it has come to make up a more and more central part of health care regulation in general, and the regulation of genetics in special. However, its pre-history in a medical context goes back to the transition from medical ethics to bioethics that took place during the 1960s. From its very inception concerned with the relationship between patient and physician in the face of technological and institutional changes, the discipline of bioethics has co-evolved with both scientific developments and social and political movements. It is therefore a good intake to the wider concerns we face at the threshold to the genomic era, some of which have been given a broad outline above.

Transforming medical ethics

For a long time, the only official articulation of the patient-physician relationship was found in medical ethics. However, the "official" status of that body of thought was peculiar, insofar as it was kept strictly within the domain of the medical profession itself (Rothman 1991; Jonsen 1998). Since the time of Hippocrates, in the 3rd and 4th centuries before Christ, medical ethics were firmly embedded in medical practice and experience, written by and for medical doctors. The ethics codes of the medical profession, often expressed in manuals of conduct on

a case-by-case basis rather than as the abstract principles of philosophers, thus corresponded closely with the actions in which they were embedded. This went for both the rules of conduct, the "bedside manners" of the physician, and for the more profound ethical duties stated in the Hippocratic Oath: "to benefit the sick and do no harm", to help the poor, not exploit patients in any way and so on. In concomitance with the general authority ascribed to the physician by society, delegating the discretionary powers to decide upon most issues of public and individual health to the single doctor, medical ethics was also fully focused on the doctor's role. In terms of more recent vocabulary: it was "paternalistic" insofar as most issues of health policy could be articulated in terms of the doctor's duties.

One particular asset of medical ethics has been that the above sketched characteristics have remained remarkably stable until quite recent times. Only in the 1960s did changes start to occur that signalled the demise of the traditional approach and the coming of the discipline of *bioethics*, through which the discretionary monopoly so long enjoyed by the doctor was challenged. Towards the end of that decade and even more so in the beginning of the next, processes of medical decision-making underwent drastic changes. Some of these changes may be seen as breaches of the socio-material contract described in an earlier chapter: Although the main authority of the medical doctor may have been his knowledge about physiology, for most practical purposes he also served as the main politician of health (Rothman 1991; Jonsen 1998). This meant that it would be the business of the single doctor to decide upon moral dilemmas that arose during medical practice: who to prioritize in case of shortage of resources; which treatments to give; who should be given treatment; sometimes also which research to be done; and even which conditions and birth defects that should lead to a child being considered a "stillbirth" (Rothman 1991). In the 1960s and 1970s, however, this monopoly of the single doctor was replaced by models of communal decision-making, in which ethicists, lawyers, other medical doctors as well as community representatives and ethics committees were included in the decision-making process. Why did this change of policy occur at that particular time in history? Why was medical ethics, for so long the sole set of rules for the physicians' behaviour, exchanged for bioethics within a time-span of only ten years?

On a general basis, the transitions in question should be seen in the light of the classical sociological distinction earlier alluded to: that from *Gemeinschaft*, or community, to that of *Gesellschaft*, or society. From organisational structures in which social action is still regulated

by community norms, situated within particular communities, to professionalized structures of abstract knowledge and action.

One main difference comes in terms of *scale*. Significantly, the *hospital* as a large unit of differentiated expertise, as well as the introduction of systems of health care, contributed strongly to significant changes in the encounter between physician and patient (Porter 1997). Although the old structures to a certain extent have been continued by general practitioners, a whole set of new actors have entered the arena: the specialist physician (only to be found in hospitals and clinics), the health economist, the health administrator, the politician, the social worker and the lawyer. This increase in scale as well as the organisational reconfigurations it accompanied must by itself be regarded as an important reason why medical ethics and medical decision-making had to change: no longer a matter of the face-to-face encounter between physician and patient, but now also a matter of complex negotiations between different professions. The whole seat of medical knowledge was, physically and geographically transformed: from the local community doctor known by most, to a differentiated and abstract system situated within that sealed-off domain called the hospital, in its turn situated within the administration and organisation of the growing health care system and the national state (Rothman 1991; Porter 1997). The encounter between patient and physician, for so long situated within the local community, was removed and de-personalised. For instance, the question of which doctor to see would traditionally be limited by which doctors were available within the particular community. Within the hospital, the question would rather be determined according to which was the diseased organ: if you have problems with the heart, you go see a cardiologist; if you break a leg, you go see an orthopaedic. Hence, although the modernisation of medicine came late: when seen from this perspective, the medical encounter has evolved along with the modernisation of traditional structures of social organisation, and pretty much in accordance with the development from community structures to societal structures of action organisation as described by Beck and Giddens (Giddens 1990; Beck, Lash et al. 1996). Says David Rothman:

"As the social distance between doctor and patient, and between hospital and community, enlarged, a sense of trust eroded. When one could no longer assume that the physician shared the same values as the patient, it seemed vital to devise and implement new mechanisms, preferably formal or even rigid, to further patients' particular wishes. It became appropriate to post on hospital walls a copy of the Patient Bill of Rights, as though the facility were a factory and its users, rank-and-file labor. Even more notably, as doctor and hospital moved apart from patient and community, the practical wisdom that the practitioner had accumulated over years of clinical experience seemed less impressive than the

wisdom that the philosopher or the lawyer had accumulated through the study of first principles. In effect, bedside ethics gave way to bioethics" (Rothman 1991:11).

Closely connected to these broader developments, we find the ones that have been particularly emphasised in this project, namely the scientific and technological developments. Here, we may start more or less within the same historical and experimental context as that alluded to in the description of bacteriology and immunology. As partially described, these developments were by themselves of immense importance:

"By the middle of the twentieth century, the medical treatment with which this traditional medical morality [medical ethics] was associated bore little resemblance to the healing practices of prior centuries. During the previous one hundred years, scientific discoveries in physiology and bacteriology had radically changed the understanding of health and disease and had begun to improve the ability of physicians to diagnose and treat their patients. Immunization prevented the deadly epidemics that had devastated populations for centuries; anaesthesia and aseptic surgery enabled direct attack on diseased organs. In 1921, insulin was discovered and quickly applied to forstall the lethal effects of diabetes; in the late 1940s the first antibiotics cured infections that had often been fatal. New mind-altering drugs attacked the most serious mental disorders. Other drugs provided new control over human reproduction. Radiology viewed the body's interior. Dramatic improvements in surgical technique, stimulated by military medicine during World War II, emboldened surgeons to enter the brain and the heart. In the 1950s, kidneys were transplanted, opening the era of organ transplantation. Over the decades 1930-1960, clinical medicine, based on a stream of scientific advances and armed with powerful diagnostic and therapeutic capacities, flourished" (Jonsen 1997).

Up until the coming of the Second World War, *research* remained of low relevance to the community at large. This was a question of scale, but it was also a question of technical feasibility: only in the pre-war period did medical technologies emerge that would be of broad social and medical significance. David Rothman comments that:

"Until World War II, the research enterprise was typically small-scale and intimate, guided by an ethic consistent with community expectations. Most research was a cottage industry: a few physicians, working alone, carried out experiments on themselves, their families, and their immediate neighbours. Moreover, the research was almost always therapeutic in intent; that is, the subjects stood to benefit directly if the experiments were successful. Under these circumstances, the ethics of human investigation did not command much attention; a few scientists, like Claude Bernard and Louis Pasteur, set forth especially thoughtful and elegant analyses. But for the most part, the small scale and potential therapeutic character of research seemed protection enough, and researchers were left to their own conscience, with almost no effort to police them" (Rothman 1991:18-19).

The war changed all this: research was intensified and large-scale projects were instigated in direct connection to the war efforts. As is not unusual in wars (Porter 1997), extraordinary opportunities for medical experiments, especially surgical, existed for the medical doctors positioned close to the battleground. But organised experiments to determine physiological

function also rose sharply during the war years and, as already described, the amount of resources invested did not go down, but rose sharply in the years following the war (*ibid.*). For the sake of the biomedical sciences, the war marked the beginning of the era of large-scale research.

A central asset of the new experimental medicine was that of experimenting on humans. Already Claude Bernard had noted the necessity of research directly carried out on human subjects:

"It is our duty and right to experiment on man whenever it can save his life, cure him, or gain him some personal benefit. The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which may be harmful to him to any extent, even though the result might be highly advantageous to science, that is, to the health of others" (Bernard 1957:101-102).

However: as research in the Nazi camps proved beyond doubt: such research may turn very ugly indeed. Although the example of the Nazis pose a particularly grim example, issuing in the Nürenberg code and the Helsinki declaration on research on humans shortly after the war, reality proved to be far more messy than presupposed in Bernard's rather optimistic account of experiments on man. What's more: Bernard, for all his prescience, did not foresee the radical challenges that would be posed to the traditional medical ethics by new invasive technologies, or, for that matter, the lengths to which certain researchers would go in order to serve science, but not the patient. During the course of post-war research, practices were allowed to continue which, when revealed, would seriously question the smooth co-existence of the interest of science and the interests of the patient:

"Long after peace returned, many of the investigators continued to follow wartime rules. Utilitarian justifications that had flourished under conditions of combat and conscription persisted, and principles of consent and voluntary participation were often disregarded. This was…the Gilded Age of research, the triumph of laissez-faire in the laboratory. Yet between 1945 and 1965 very few investigators or their funders took note of the changed circumstances. The thrust of public policy was not to check the discretion of the experimenter but to free up the resources that would expand the scope and opportunity for research" (Rothman 1991:51).

One reason for this has been hinted at already: prior to the war, research had been mainly therapeutic, sometimes also diagnostic. But experimentation on humans for the sake of the abstract and objective body of physiological knowledge: that was a new phenomenon, and most scientists did not spot the slippery slope until scandal hit the media (Jonsen 1998).

One significant event was the publication of a paper called "Ethics and clinical research" by Dr. Henry Beecher, professor at Harvard. In that paper, which did not go home well in the biomedical research community, Beecher gave examples of 22 cases in which "unethical" experiments had been carried out on humans without their expressed knowledge of the risks involved, and without the giving of informed consent. These, however, were mere examples of what Beecher estimated to be "widespread problems". In the face of grave critique, amongst them that of "blocking progress" (Beecher 1966), Beecher argued that the old ethics code had transgressed it's borders and that informed consent be made obligatory to research on humans. Beecher began his article by referring to the shear growth in public funding that had taken place in the post-war era: between 1945 and 1965 NIH funding of research multiplied by 624 (*ibid*.).

In 1962, the Thalidomide scandal hit the media, revealing severe adverse effects of sleeping pills to the off-spring of mothers who had used the pill to ameliorate minor afflictions of early pregnancy. Merrell Pharmaceuticals was forced to withdraw the product from the market the very same year. And in 1972, the Tuskegee affair was announced by *The New York Times*: 600 men of Afro-American origin, most of low income and education, coming from Tuskegee in Alabama, had been used as guinea-pigs in research on syphilis. The men had been promised rewards like free meals and medical care, but were not informed that they had syphilis and were not offered any treatment (as that would interfere negatively with the design of the research) (Jonsen 1998).

Although both the rapid growth of scale in research and health care and revelations of experiments on humans were strong promoters of an ethical awareness, one will have a hard time arguing that they were sufficient conditions for the changes that were about to take place. They should also be seen as part of very general tendencies following the war in which human rights came to heightened attention, increasing wealth in western societies, and so on. But there were also "purely" technological developments that, as if by themselves, radically expanded the scope of medical interventions and so opened up for a range of unprecedented (moral) choices. I mention two:

- In 1961, the *dialysis* machine was introduced into medical practice. By inserting a plastic tube (well-known from every modern hospital), the machine would substitute for impaired kidney functions in the patient, allowing for lives to be prolonged.

Although a highly useful invention, the procedure was expensive and scarce, and so the question of how to prioritise among patients arose. In addition came the hard question of how long to prolong life when the patient was no longer responding to external stimuli: life and death had to be redefined for the sake of medical decision-making. In this process, medical doctors were not the only obvious authorities, and so contributions from theologians and philosophers gradually came to be accepted, and after a while even required (Rothman 1991; Jonsen 1997).

- Some of the previously described developments within immunology had solved the problem of graft rejection in cases of organ transplantation, leaving the way open for matching types of tissue to be transplanted to patients in need of new organs. In terms of moral dilemmas and medical policy, this case proved even harder to settle: Was it right to remove organs from dead or dying persons? And, as can be imagined, here resources were even scarcer: who were to be given the few organs that became available? In addition came the fact that early experiments on transplantation were of an experimental nature, and so could imply serious risks for the patient (Jonsen 1997).

A political consciousness?

As many of the infringements through human experimentation were directed at minorities, they went hand in hand with the broadened political consciousness and activism of the late 1960s, and with the rights movement in particular:

> "In fact, the agitation over human experimentation quickly became linked to the rights movement that were gaining strength in the 1960s, largely because the great majority of research subjects were minorities, drawn from the ranks of the poor, the mentally disabled, and the incarcerated. This linkage ensured that the rights of research subjects (or, conversely, the felt need to restrict the discretion of the researcher) would not only capture but hold public attention" (Rothman 1991:10).

Many parallel developments, political, institutional and technological, contributed to an urgent need for rethinking the relation between patient and physician, patient and system, patient and research. Not only was the medical ethics of old conceptually inadequate; both patient and physician had been thrust into a new and more complex situation, one in which the old face-to-face ethics could do little to help the many difficult choices and restructurings that would have to follow. Through specialisation, up-scaling and rationalisation, the doctor had become "a stranger at the bedside" (Rothman 1991).

With increasing specialisation and with more resources invested in basic research, more and more doctors would go into research. In many cases, i.e. where research was aimed at establishing an objective body of physiological knowledge rather than helping therapeutics or diagnostics in the concrete case, developments risked positioning the interests of the doctor, and of objective scientific knowledge, *against* the immediate interest of the single patient. As this transformation was not conceptualised, but rather tacitly introduced under the supposition that the doctor-researcher would by himself be capable of overseeing and regulating the ethical, legal and political issues involved, revelations of misconduct in the name of science struck hard within academic, public and political spheres. Clearly, the medical researcher was *not* up to the challenges of the new policies of health, and clearly his time as sole authority in questions of health policy had to come to an end. Something very similar also went for the new moral dilemmas created by developing technologies.

Hence, what took place was very much that the old political and ethical problem of the individual's relation to society in general found its way into the medical arena, where it had to be re-negotiated. In the words of the philosopher Hans Jonas, one of the strongest and most original contributors to the debate:

"…we require a careful clarification of what the needs, interests, and rights of society are, for society – as distinct from any plurality of individuals – is an abstract and, as such, is subject to our definition, while the individual is the primary concrete, prior to all definition, and his basic good is more or less known. Thus the unknown in our problem is the so-called common or public good and its potentially superior claims, to which the individual good must or might sometimes be sacrificed, in circumstances that in turn must also be counted among the unknowns of our question…" (Jonas 1969).

In terms of the socio-material contract, the medical doctor had been invested with political responsibilities, and so the main legitimacy of this investment stemmed from the domain of the natural, and not from the political sphere. As medical and technological possibilities expanded drastically, the discretion given to the doctor in defining the central issues of health policy was also challenged. In that way, the doctor was driven in the direction of his main area of expertise, namely the technical and scientific domain, whereas other groups would increase their influence over what came to be seen as the *ethical* domain. These developments went hand in hand with the increasingly strong scientific basis for the understanding of disease. Science and technology, -for all the good they have accomplished, have also worked hard to dispel sources of uncertainty, -among them the patient, from the domain of the medical doctor. Modern medicine, in endorsing a scientific basis, may do itself a disservice if

scientific and technical developments should persist to dispel the humanistic side of the profession. In the view of one prominent practitioner and philosopher:

> "The uncomfortable fact remains that doctors cannot get at diseases without dealing with patients – doctors *do not treat diseases, they treat patients*. Further, the same disease in different individuals may have a different presentation, course, treatment and outcome depending on individual and group differences among patients – from personal idiosyncrasies to genetic or anatomic variations. The scientific basis of medicine does not recognize nor provide a methodology to deal with such individual variations on the level of patient-doctor interactions. Such issues were relegated to the "art" of medicine or to individual judgement" (Cassell 1991:19).

During the 1960s, a growing number of theologians, physicians and philosophers had started to concern themselves with the ethical dilemmas of medical decision making. The issues brought forward were often very broad, sometimes speculative, and more often than not ill-suited to supply solutions to a field in which demands were continually raised that decisions be made fast or not at all. Not the least, this was a consequence of the practitioners from these fields struggling to adapt abstract and theoretical disciplines and concepts to the realities of the clinic or the laboratory. If bioethics was to replace the scientific and medical definitions of "the public good", it had better be done in terms that could actually cast a light upon concrete cases so as to facilitate and improve decision-making.

During the 1960s, organised attempts at doing bioethics would generally stretch to arranging conferences in which wide arrays of topics were aired and discussed, often in close connection to the political climate of that period. As already mentioned, the close vicinity to the civil rights movement was particularly important. But in terms of concrete recommendations for policy-making, the outcome was modest (Ach and Runterberg 2002). However, by the end of that decade, developments took place that would eventually lead bioethics towards firmer disciplinary grounds, thus also leading its practitioners to establish more stable and concise vocabularies and working methods. Most important in that respect: the problems generated in medical research and clinical practice, and the increasing public attention received by these developments were noted and responded to by politicians.

In 1968, developments in genetics and heart transplantation led Senator Walter Mondale (Democrats Party) to instigate political hearings to probe the grounds for establishing a Presidential study commission The mandate of the commission would be to study "organ

transplantation, genetic engineering, behaviour control, experimentation on humans, and the financing of research" (Jonsen 1998, 91). Whereas the actors already involved in these questions would be positive (i.e. theologians, philosophers, sosiologists, lawyers), the invited scientists and medical doctors were generally reluctant, where not downright hostile, towards the idea. Because of stark opposition from these groups, the 1968 proposal came to nothing (Rothman 1991).

Mondale, however, did not give up, and so raised the issue again in 1971. Also this time, opposition was strong, and Mondale remained perplexed by the reception of his proposal:

> "all we are proposing here is to create a measly little study commission to look at some very profound issues…I sense an almost psychopathic objection to the public process, a fear that if the public gets involved, it is going to be anti-science, hostile and unsupportive", Mondale quoted from (Jonsen 1998:94).

Eventually, Mondale's views won out and his attempts issued in the creation of the Advisory Commission on Health, Science and Society in 1973. The expression of "ethical, legal and social" consequences, later to be found in the periphery of genomic research, stems from Mondale's efforts to establish this commission (*ibid.*).

1973 saw another political hearing, initiated by Senator Ted Kennedy, who was expressing concerns similar to those raised by Mondale. At this stage, the issues of genetic engineering, reproductive technologies, research on foetuses and un-knowing subjects had ignited the attention of other senators and politicians as well. Hearings were held, involving central scientists (among them James Watson) and bio-ethicists (such as Dan Callahan), and other hearings were devoted to specific issues, like human experiments and the Tuskegee revelations. A National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was instigated (*ibid.*).

I now turn to the development of regulatory bodies instigated to replace the traditional structures of medical decision-making that followed in the wake of the above political events. Centrally, I give a description of some of the concepts developed in and around these new institutions, concepts that would come to play important roles in the future structure of bioethics. As we have seen also in other young disciplines, the development of a (more or less) specific method, of a conceptual framework as well as proper institutions, went hand in

hand with the development of the discipline as such. Of special importance: towards the end of the 1970s, *autonomy* emerged, not as the Archimedean point around which everything else revolved (we are dealing with language here, and not with a technological object), but still as the central organising principle of bioethical thought and action.

Defining the concepts, defining the discipline

The many revelations of unethical research, both in the laboratory and in the clinic, forced the NIH, as the main funding agency of biomedical research in the United States, to take decisive steps in order to counter criticism and to improve the situation. In 1966, under the lead of the Department of Health, Education and Welfare, a set of guidelines were issued in which the responsibility for research was delegated to the single institutions receiving the funding and carrying out the research (Rothman 1991, 89). Importantly, the institutions themselves were to control that the *informed consent* of the research subjects or the patients was given. The concept of *voluntary* consent had been defined in the Nuremberg code:

"…the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment".

In the Helsinki declaration, the conception of informed consent was used expressly. However, in terms of social organisation it remained abstract, i.e. it was not connected to any institutions in particular. The concept was first deployed for purposes of public decision-making in a court ruling in 1957, in which it was ruled that physicians "have the duty to disclose any facts which are necessary to form the basis of an intelligent consent by the patient to proposed treatment" quote from (Jonsen 1998:355).

In the above cited cases, however, it had been the responsibility of the researcher or the clinician to see to it that the correct procedures were followed. As seen, this was not sufficient. In this respect, the issue at stake was not that of accepting informed consent or not, but rather on *whom* the responsibility was put for the right procedure to be followed. The NIH and the Department of Health came up with the idea that the institutions themselves be made

responsible, and that this responsibility was to be shared among a group of individuals, a committee or the like, acting on behalf of the patient:

> "Safeguarding the rights and welfare of human subjects involved in activities supported by grants or contracts from the Department of Health, Education and Welfare is the responsibility of the institution which receives or is accountable to the DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of the department that no grant or contract for an activity involving human subjects shall be made unless the application for such support has been reviewed and approved by an institutional committee" (Department of Health, Education and Welfare 1971).

By this move, the transfer of discretional powers from the physician to a larger community was officially undertaken. However, the responsibility had not really been moved out of the physicians' domain: the committee in question was to be composed of peer scientists or clinicians. As described by Rothman: although ground-breaking, the move had something defensive about it. It could also be regarded as an attempt to respond to public scrutiny while still keeping discretion within the medical and scientific community. Hence, the guidelines "…retained an investigator's scepticism about the ultimate value of the procedure, a position that was widely shared in the research community." (Rothman 1991:91).

However, the political initiatives already under way would see to it that groups and professions outside of the biomedical communities would soon be instigated as guardians of patients' rights. Following the Kennedy hearings in 1974, the National Research Act was signed by President Nixon. The act instigated the aforementioned National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in a direct position towards the Department of Health, Education and Welfare. The Secretary of that department was to respond directly to the recommendations of the commission. If the secretary chose not to do so, he would have to answer to the Commission (Jonsen 1998). The commission consisted of lawyers, theologians (among them Albert Jonsen), philosophers, physicians, biologists and one representative from the public (*ibid.)*. The eleven members were instructed to "recommend to the Secretary of DHEW regulations that would protect the rights and welfare of human subjects of research, particularly with regard to informed consent and institutional review of research" (*ibid.,* 100).

Hence it was that a new balance was sought out between society and research in which the respect for individual rights was instigated as the main point of reference. Furthermore, the

rights of individuals were to be conceived in terms of ethical principles. The mandate of the commission was to "identify the basic ethical principles that should underlie the conduct of biomedical and behavioural research involving human subjects and develop guidelines that should be followed in such research" (*ibid*.). In the years to come, a number of guidelines issued from the Commission, dealing with subjects such as institutional review boards, research involving children, prisoners and the mentally ill; health services in general, and disclosure of research information. The commission would typically work by hearing both public opinion and expert advice, discussing the relevant issues among its members, finally to settle upon the best solution as they saw it. Significantly, their working methods distinguished themselves from ordinary academic deliberation and analysis by the practical-political dimensions involved: concrete solutions to concrete problems had to be arrived upon within given time schedules (*ibid*.).

The most significant outcome of the commission's work was instigated in 1976 when they were asked to comment on the principles that should underlie biomedical research in general. The initial report was finished the same year, but it continued to be revised throughout the next three years. In 1979 it issued as *The Belmont Report*, which has since become a cornerstone of bioethics and the regulation of biomedical research.

The Belmont Report

In accordance with what has previously been stated about legitimate sources of knowledge in modernity: technological and institutional progress brought to the fore sharpened principles of universality in both the natural and social domains. This, in turn, facilitated a sharing of work in which the technical and scientific was separated from the ethical decisions involved in medical decision-making. The Belmont Report specified three ethical principles in order to provide "a basis on which specific rules may be formulated, criticized and interpreted": Respect for persons, Beneficence and Justice. These three basic principles were regarded as leading to three corresponding requirements of practical application: informed consent, risk/benefit assessment and selection of subjects for research.

The first thing to notice here is the explicit endorsement of ethical principles rather than rules and precepts, a transition best explained by recourse to the increasing complexity and value pluralism of modern societies. Recall how, in the chapter on methodology, I referred Ronald Dworkin's critique of Herbert Hart's picture of law: defining law as dealing mainly with rules

of conduct, it leaves out a number of more complex situations in need of interpretation and judgement. Hart's picture, says Dworkin, has to be complemented with a basic understanding of the role of principles in organising human action. The distinction made by Dworkin should not be seen as analytic only; it may also be regarded as a sociological distinction emerging along with the increased complexity of society in the twenty years or so after Hart wrote his book. Something parallel may be stated about ethical codes of conduct for research and the clinical encounter. Referring to the Nurnberg Code, the National Commission wrote that:

"The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or to apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted" (National Comission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979).

The first principle of the report was that of "respect for persons". Through this conception, strongly reminiscent of Kant's categorical imperative[72], the institute of informed consent was given a firmer philosophical foundation, namely "respect for persons". The conceptions of respect and personhood, however, were not clarified, but rather directly translated into the concept of autonomy:

"Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy. An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation" (National Commission for the Protection of Human Subjects of Research 1979).

In practice, respect for autonomy spelled out as the giving of the proper information to the research subject, that he or she comprehended the relevant information, and that he or she entered into the research project voluntarily. The language of the report was influenced by philosophers like Hans Jonas, Paul Ramsey and H. Tristram Engelhardt, who all sought to elevate the single individual above the utilitarianism of research in the 1960s and 1970s: one

[72] The categorical imperative was given in many different versions by Kant. One articulation that captures the motivation of the early bioethicists particularly well is the following: "Achtung geht jederzeit nur auf Personen, niemals auf Sachen", KpV, A 136. Translated into the problem of research on human subjects, this principle of respect denies the ascription of value to abstract bodies of knowledge, while endorsing the value of the "concrete individual" (Jonas).

individual's worth was not to be subordinated to the (allegedly) greater goal of common welfare through research. Obvious to philosophers: Kant's dictum to treat the subject as an end, and never purely as a mean, exerted strong influences on the solutions found by these early bioethicists (Jonsen 1998). Hence it was that autonomy was instigated at the centre of the bioethical discourse. What had been initiated as a demand for informed consent from research subjects had been given a more philosophical and principled foundation.

The three principles in question had been selected out from a rather long list of possible candidates, for instance: "respect self-determination, benefit individual research subjects, benefit other individuals and groups present and future, minimize harm to individual subjects, minimize consequential harm to others, and attend to distributive justice and to compensating justice" (Jonsen 1998:103). Although not stated in the report itself, one reason for excluding these and to keep those of respect, beneficence and justice, was that these were seen as universal principles proper (*ibid.*). Furthermore, they were comprehensive and "stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects" (National Commission for the Protection of Human Subjects of Research 1979).

The principle of Beneficence had been derived from the Hippocratic maxim to "do no harm". Claude Bernard was cited as bringing the principle into the domain of experiments on human subjects. Now, the principle was translated as obliging researchers and their institutions to "give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures" (*ibid.*). When applied to practice, then, the principle of beneficence, itself derived from the older precept of doing no harm, spelled out as the proper assessment of risks and benefits:

"The requirement that research be justified on the basis of a favourable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons" (*ibid.*).[73]

[73] Philosophically speaking, this inference is problematic. In terms of positive precepts for action, *nothing* can be derived from the principle of autonomy itself; it is a wholly negative and limiting concept (Wellmer 1986). In short: whereas we may use the concept of autonomy or respect for excluding actions and reasons as not respecting autonomy, we cannot, strictly speaking, derive anything from these principles.

Although the limitations of quantifying risk/benefit analyses were noted, it was stated that the "idea of systematic, non-arbitrary analysis of risks and benefits should be emulated insofar as possible" (*ibid.*) in order for the communication of risks and benefits to proceed as smoothly as possible between the involved actors, notably the members of the review boards and investigators.

This transformation of the precept to do no harm into the principle of beneficence, which was next translated into the practical precept of proper risk/benefit analyses, illustrates a general point of this project: during the process of modernisation, basic categories of action and choice lose many of their "traditional" qualities and properties, which are then transformed into more or less standardising principles. Heightened efficiency may come at a price, namely to strip basic ways of understanding and acting of their commonly shared properties in favour of counterfactual presuppositions about agency. In the case of bioethics and its central concepts, this inherent mechanism of modernisation constitutes something of an irony: initially instigated to empower the individual in the face of an increasingly powerful medical system, demands for disciplinary consistency and efficacy in the face of decisions needing to be made fast requires conceptual tools that are universal and quantifiable. But this raises the demand for new kinds of expertise to help the individual assess the risks and the benefits of the situation, and so the democratic problem is reproduced. In one early statement of what bioethics was supposed to be, Daniel Callahan wrote that:

"…it is of the essence of moral decision-making to be couched in ordinary language and dealt with by ordinary, non-professional modes of thinking. The reason for this is apparent. An ethical decision will not be satisfactory to the person whose decision it is unless it is compatible with the way in which the person ordinarily thinks about himself and what he takes his life to be" (Callahan 1973)

At the same time, Callahan, somehow unintentionally, gave testimony to the tangle in which bioethics and its central concepts (already) found itself:

"My contention is that the discipline of bioethics should be so designed, and its practitioners so trained, that it will directly – at whatever cost to disciplinary elegance – serve those physicians and biologists whose position demands that they make the practical decisions" (Callahan 1973).

Hence, we see that bioethics, although seeking to articulate the interests of the patient, early on came to rely upon the understanding of reality as offered by scientists and medical doctors.

It is understandable that Callahan, in 1973, would argue like this, -his main purpose perhaps not so much to reinvest the experts of the biomedical community with the power to define the interests of the patient, as to free the nascent discipline of bioethics from its mother discipline, philosophy, in which argumentative rigour and abstractness were (and are) cultivated for their own sake:

> "If ethics was nothing other than seeing to it that no logical fallacies were committed in the process of ethical argumentation, it would hardly be worthy of anyone's attention. It is the premises of ethical arguments, the vision behind ethical systems, the feelings which fuel ethical (or non-ethical) behaviour, which make the real difference for human life. Verbal formulations are only the tip of the iceberg. An ethicist can restrict himself to that tip; he will be on safe enough professional grounds if he does so. But I see no reason why he can't dare more than that, out of a recognition that the source and importance of his field lie not in the academy but in private and public human life, where what people think, feel and do make all the difference there is…" (Callahan 1973).

Last, there was the principle of justice, of which I will not say much. It was introduced to the Committee by Tom Beauchamp (Jonsen 1998), who was building upon John Rawls idea of distributive justice: "An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly" (National Commission for the Protection of Human Subjects of Research 1979). In practice, this principle was to see to it that subjects of research were not selected in an unjust manner. Specifically, as in the Tuskegee scandal, it was important that the subjects were not taken from poor segments of the population or from minorities poorly situated to make their interests noted. This does, however, remind us of the context in which the Belmont Report arose, of which I will have something more to say in what follows.

Some legal interventions

The increased political attention devoted to the rights of research subjects found its counterpart in legal developments that would make their way into the clinical encounter more directly. Whereas the issue of research on humans gradually came to revolve around the rights of the single patient to be protected by communal modes of decision-making, i.e. ethical review boards, the courts now instigated themselves as protectors of the patients' welfare.

During the late 1970s and early 1980s, the legal relationship between physician and patient, and between hospital and patient, came to the fore with particular force in cases of life-sustaining technologies. In the perhaps most well-known case, Karen-Ann Quinlan was kept on respiratory machinery and nourished through a tube while in a comatose state. According

to technical jargon she was not brain-dead, and so it was decided that she be kept alive. The decision was opposed by her Catholic family as well as the community to which they belonged, claiming for her father to be instigated as her guardian and that she be granted the right to die. In the ruling, it was judged that Karen-Ann had a right to privacy and that her father had the right to be instigated to make decisions on her behalf. Furthermore, and most important for the present purpose: the court, realising the complexity of the matter, set forth the proposal that future decisions in right-to-die cases be delegated to ethics committees composed by a wide variety of members, such as lawyers, theologians, social workers and theologians (Jasanoff 1995). In the years to come, a number of cases were raised in which the principle of autonomy and ways of communal decision-making were negotiated. American courts actively interfered in order to strengthen the rights of the individual. Although thereby provoking new problems, Jasanoff concludes that

> "On balance…the courts dealt with the social impacts of life-sustaining technologies in ways that furthered the development of collective norms and of new institutional arrangements with respect to death and dying. Following Quinlan, courts successfully delegated to ethics committees the responsibility for micromanaging right-to-die decisions" (*ibid.*,202).

Also according to David Rothman, the incision of the courts and ethics committees into the clinical relationship was to be seen as a necessary and legitimate move in the face of growing technological possibilities and an increasingly powerful medical profession, rather than a professional take-over: "…lawyers and judges had not pursued some imperialistic imperative and invaded medicine's domain but, rather, were in alliance with patients in an effort to right an imbalance of power and establish the principles of patient autonomy" (Rothman 1991:232).

Bioethics as a discipline

During the 1970s, the rudimentary character of the bioethics debate of the preceding decade was replaced by more ordered and scholarly disciplined institutions of biomedical research. Following Albert Jonsen, I here refer the development of two central institutions, namely those of The Kennedy Institute and The Hastings Center.

The Hastings Center was founded in 1970 by Daniel Callahan. Originally trained as a philosopher and working for a Catholic journal, he got himself involved in bioethical matters while trying to come to terms with the question of abortion. Receiving generous support from organisations such as the Rockefeller Foundation, the National Endowment for the

Humanities as well as single donors, the Center soon grew to encompass a highly resourceful and interdisciplinary staff, consisting of philosophers, physiologists and theologians (Jonsen 1998), 21. Due to the funding, the center remained independent of academic institutions, an important factor for the success of the institution in its operations on the interface between lay public and experts, and between theoreticians and practicing physicians and scientists. Sharing work between them, four study groups were established, one of which dealt specifically with genetic engineering and counselling. The others were on population control, death and dying, and on behaviour control (*ibid*.). In 1971 the publication *The Hastings Center Report* appeared, which to a large degree served to shape the discipline to come: "The index of the *Hastings Center Report* over the next years defines the range of topics that were becoming bioethics and constitutes a roll call of the authors who would become its proponents" (*ibid*.). In 1971, the center contributed to the organisation of a conference on "Ethical Issues in Genetic Counselling and the Use of Genetic Knowledge" (*ibid*., 22).

Also the *Kennedy Institute*, which was founded in 1971 by André Hellegers, grew out of a mixture of theological and philosophical concerns with abortion and the new possibilities offered by reproductive medicine. The name was chosen because of the source of its funding, the Kennedy Foundation. In contradistinction to the Hastings Center, the Kennedy Institute was closely connected to an academic institution, Georgetown University, and so the institute, from the outset run by theologians, came to take the more scholarly path of the two. Significantly, a library consisting of bioethical texts was collected (by Leroy Walters), and every year a bibliography of newly published texts was published. Eventually, these sources issued in a national reference center for bioethical literature, securing for the first time a collected body of bioethical works. A graduate program was also instigated in cooperation with the philosophy department, and by the end of the 1970s bioethicists were regularly out-examined from the institute (*ibid*.).

The most significant work to come out of the Kennedy Institute was Beauchamp and Childress' *Principles of Biomedical Ethics*, the first edition of which appeared in 1977[74]. Since that time, the book has become something of a standard in bioethics (Jonsen 1998). The book states four main principles as the basis of bioethical discourse and deliberation: autonomy, nonmalificience, beneficience and justice. As seen, three of the principles are the

[74] The following remarks will not be based upon that edition, but on the revised (fifth) edition from 2001.

same as those given in the *Belmont Report*; only nonmaleficience has been added. The set of principles, the authors tell us, is not intended to serve as a coherent moral theory; in many cases they may be at odds with each other. As the purpose of the book is practical rather than theoretical, this state of affairs is not attempted resolved, but rather taken as an expression of the often contradictory and incoherent character of real-life moral decisions and of common morality: "A set of principles in a moral account should function as an analytical framework that expresses the general values underlying rules in the common morality. These principles can then function as guidelines for professional ethics" (Beauchamp and Childress 2001:12). Furthermore, either of the principles is intended as prior to or overriding all of the other principles. Concerning autonomy, the authors specifically underlines this point in order to counter allegations of them being promoters of the "triumph of autonomy" (Veach 1984).

Be that as it may: quite independently of how Beauchamp and Childress intended their own work to be perceived, there can be little doubt about the central position of the concept in the following years (this is especially so for the American context, but parallel developments have also taken place in Europe). Autonomy, and its counterpart informed consent, emerged at the centre of biomedical practice: in institutional review boards, ethics classes, ethics committees, in the laboratory and in the clinical encounter (Veach 1984; Dworkin 1988; Ach and Runterberg 2002; O'Neill 2002). Thus, in many ways, the history of bioethics, especially up until the eighties, was a story of success. During a span of ten years, the medical decision-making process was transformed. Here was an example of a social order being established by a number of groups, -scholars, lawyers, politicians, medical doctors and activists, in the face of new technological and ethical challenges. Perhaps most importantly, the movement initiated through bioethics corresponded with and responded to wide social concerns of the times:

> "In the end, the initial commitment of bioethics to patient rights helps account for its extraordinary accomplishments in the decade from 1966 to 1976. The fit between the movement and the times was perfect. Just when courts were defining an expanded right to privacy, the bioethicists were emphasizing the principle of autonomy, and the two meshed neatly; judges supplied a legal basis and bioethicists, a philosophical basis for empowering the patient. Indeed, just as when movements on behalf of a variety of minorities were advancing their claims, the bioethicists were defending another group that appeared powerless – patients" (Rothman 1991:245),

One particular fact, says Rothman, also secured the continued acceptance and legitimacy of the demand for increased patient autonomy, -and singled it out as a special case among many

other causes championed by the rights movement in general, -namely its applicability across class lines: “Not everyone is poor or a member of a minority group or disadvantaged socially or economically; but everyone potentially, if not already, is a patient” (*ibid*., 246). Hence, the *language* in which the bioethicists articulated their agenda found wide acceptance among differing social groups and classes. The typical bioethicist may not greatly have resembled the average social activist of the day; bioethicists often came from academic and catholic backgrounds, and many would go to great lengths to distance themselves from what they perceived to be leftist activism. Still, the case remained that there were also strong parallels between the two movements and that these went well with the political and legal climate of the time. Bioethics gained in strength and relevance from these shared structures of public action and discourse (Rothman 1991; Jonsen 1997; Ach and Runterberg 2002).

Bioethics and the genome

I now continue by connecting the above discussion to the one carried out in the chapter “The genome and the clinical context”. The significant point is how the principles originally designed to guide research on human subjects also came to exert their influence on other fields, significantly that of the clinical context. As stated by Albert Jonsen about the general significance of *The Belmont Report*: “Its principles found their way into the general literature of the field, and, in the process, grew from the principles underlying the conduct of research into the basic principles of bioethics” (Jonsen 1998:104). However, as will be seen, there are reasons for doubting the adequacy of the concepts of autonomy and informed consent when transferred to the clinical encounter. This is especially so with genetics and genomics, as the problems posed by these disciplines are of such novel and, in many cases, un-precedented character. These cases, I take it, are particularly powerful inducers of the dilemma instigated by the socio-material contract and the following delegation of discretionary powers to experts: in the case of doubt and uncertainty, the main sources of legitimacy in modernity are called upon to facilitate decision-making. These, however, are articulated in terms of universal principles of physiological function (nature) or universal ethical principles, i.e. counterfactual organisers. But how can decisions based upon such premises, as prescribed by Callahan, be “satisfactory to the person whose decision it is”?

The Belmont Report started out by clarifying a distinction that had underpinned the bioethical debate from its inception, namely that between “clinical application” and “research”. The relevance of the distinction has already been indicated. In the above quote from Hans Jonas,

we saw that he specifically forwarded "the individual as the primary concrete". It was the establishment of abstract bodies of objective knowledge through biomedical research that was in need of justification when positioned towards the concrete individual. The main rationale behind this shift of emphasis was that the public or common good could no longer be equated with scientific knowledge.

"It is important to distinguish between biomedical and behavioural research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research…For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioural practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships)" (National Commission for the Protection of Human Subjects of Research 1979).

The committee clearly realised that in many cases the boundary between the two would be blurred. But in practice, it was surmised, this did not constitute a major obstacle: "if there is any element of research in an activity, that activity should undergo review for the protection of human subjects" (*ibid*.).

For the purposes of this project, the above distinction is of importance: the notions of informed consent and autonomy entered the policy scene as mechanisms for regulating research on human subjects. Clinical practice, mainly regarded as therapeutic in character, was not subjected to ethical review. In spite of this: In a previous chapter ("The genome and the clinical context"), we saw how, in the late 1970s/early 1980s, the concepts of autonomy and informed consent were already emerging as boundary-regulating tools in the new constellations of the clinical encounter offered through genetic screening and testing. It was clearly recognised that these practices were experimental in character, and so their socialisation required that one proceeded in a cautionary manner. However, in the 1983 report *Screening and Counselling for Genetic Conditions: A Report on the Ethical, Social, and Legal Implications of Genetic Screening, Counselling, and Educations Programs*, there is no mention of submitting these practices to ethical review boards. In stead, responsibility is left by and large to the professionals:

"Much of the responsibility for establishing and enforcing performance standards for a particular test will fall to the professions themselves. Nevertheless, public officials, including those who fund

programs or regulate screening products, share responsibility for seeing that the test is used in a way that will maximize benefit and minimize harm" (The President's Comission 1983).

In all the three cited reports on genetic screening, the regulatory problems connected to those practices are underlined in the introductory passages. To quote the most recent, *Assessing Genetic Risks: Implications for Health and Social Policy*:

"The committee took its starting point from the wise advice of the 1975 National Academy of Sciences Study *Genetic Screening: Programs, Principles, and Research*: [quote 1975 report] Screening programs for genetic diseases and characteristics…have multiplied rapidly in the past decade, and many have been begun without prior testing and evaluation and not always for reasons of health alone. Changes in disease patterns and a new emphasis on preventive medicine, as well as recent and rapid advances in genetics, indicate that screening for genetic diseases will become more common in the future. These conditions, together with the mistakes already made, suggested the need for a review of current screening practices that would identify the problems and difficulties and give some procedural guidance, in order to minimize the shortcomings and maximize the effectiveness of future genetic screening programs [end of 1975 quote]. These words, written almost 20 years ago, remain just as valid today for genetic screening and diagnosis" (Institute of Medicine 1994).

Thus, it could hardly have been that problems connected to genetic screening and testing were not recognised. Furthermore, it is hard to believe that these practices would not qualify as containing elements of "research" according to the definition of the Belmont Report: already the 1975 report stated the necessity of proceeding in an "experimental mood". Developments in genetics and health care emerged during the same period as ethical review boards were instigated to take care of the interests of the patient in research facilities and hospitals. Still, the general rule that discretional power be transferred from the physician to review boards and patients did not seem to apply fully to the cases of genetic screening and testing. Here, the responsibility was left more or less in the hands of the clinician, the genetic counsellor, and the patient. *One* reason for so doing lay in the fact that the early transgressions and mistakes made in screening programs were regarded as mistakes made by individual researchers in a new and developing field:

"Most of the mistakes, most of the ethical transgressions, most of the failures to observe people's rights, most of the breaches of confidentiality and informed consent and so on occurred early on when screening was being done by individual investigators or by interested lay groups, when it was being done in inappropriate places, and before the network of educators, counsellors, physicians, health officers, and the like were set up" (The President's Comission 1983).

One further reason no doubt resided in the positive value generally ascribed to genetic information and the optimistic view of people's capabilities of making autonomous and informed choices based on that information:

"Genetic screening and counselling have the same central purpose: to make people into informed decisionmakers about their genetic constitution, to the extent that it is relevant to their own well-being or that of their family" (*ibid*.).

In the context of genetic medicine, then, the concern that the patient be threatened from an increasingly powerful medical system seemed to have evaporated. Again, the individual and his/her autonomy were invoked, but this time the function was not defensive; it was rather affirmative. The autonomy of the patient as well as proper professional procedures would see to it that genetic screening and testing would turn out for the better: to society, to the patient and to science and medicine. Was this a return to pre-Belmont conditions, or was it rather a harbinger of things to come, of problems not articulated within the fast established bioethical cannon?

I will let Albert Jonsen answer the question. Speaking of bioethics' relation to technical, social and medical developments in the period 1987 to 1997, he states that:

"During the decade since 1987…the discipline and discourse have…changed direction in significant ways. Any field that comments on actuality, as bioethics does, is necessarily moved by events and inventions, and the decade has been filled with advances in medical science as well as new forms of health care delivery and policy, that called for commentary. At the same time, the leading ideas that form the discipline have come under scrutiny; the theory, principles and practices that evolved during the first decades do not seem to measure up to the new questions" (Jonsen 1998:406).

Not surprisingly: among the new questions referred to by Jonsen we find those connected to the launching of the human genome project. When regarding autonomy and informed consent in a wider social and political setting, it becomes clear that these concepts, when uncritically transposed to new contexts, such as that of genetics and the clinical encounter, takes on different functions from those originally intended. The reason for this, as marked by Jonsen, is as simple as it is complex: the surrounding context has changed significantly, and so there seems to be an increasing gulf between concept and reality. As also seen in the chapter on patentability, this is connected to the changes within the sciences themselves, to the scientific

object becoming information, and to the objects' new role within an ever faster-moving information economy: "…the contexts in which consent or dissent might be sought or given are changing in ways that may stretch, strain and perhaps overwhelm individuals' capacities to give informed consent" (O'Neill 2001).

Centrally for our purposes: the concepts of autonomy and informed consent were conceived of within a context of research. Where expanded to the clinical context, it was mainly conceived of within an understanding of the clinical encounter as mainly therapeutic in character. Hence, in *Principles of Medical Ethics*, it is held that "An informed consent is an individual's *autonomous authorization* of a medical intervention or of participation in research" (Beauchamp and Childress 2001). Within this understanding of the clinical encounter, the information part of the definition is still conceived as directly related to some physiological intervention to be undertaken. But how does this look when the information *is* the intervention?

Informed consent was initially instigated to replace the exclusive authority of the medical researcher for communal forms of decision making, a task that by most measures was well performed (Rothman 1991; Jasanoff 1995; Jonsen 1998). However, within the context of genetics (and genomics) these concepts may even be said to have *the exact opposite effect*, namely that of ascribing to the patient, *qua* rational decision maker, the moral responsibility for the risks of his or her condition. If that is the case, bioethics cannot be said to counter or to make problematic technological and medical developments, but rather to confirm and strengthen them. As long as the autonomy of the patient is respected through the taking of his or her informed consent, the ethical responsibility of the medical doctor or the health care system has been taken care of. What remains is the scientific and technical responsibility of providing correct information as the basis of the decision to be taken by the patient. The intrinsic norm of *non-interference* of the geneticist or counsellor with the patient's decision confirms this new sharing of work. Hence: because genetic information is regarded mainly as a good, the institute of informed consent promotes and projects the construction of the single individual as an "informed decision maker about his or her genetic constitution".

The problematic status of autonomy and genetic information

It thus seems that autonomy and genetic information end up by working together in projecting the patient as a rational decision-maker, one capable of making autonomous choices based

upon proper information about his or her genetic constitution. Although in this project that transfer of responsibility is regarded as problematic, this may not be the prevailing view in policy formation or mainstream bioethics. As seen from the above quote from The President's Comission: presupposing the general utility of genetic information as well as the capacity of the patient for autonomous choice, this state of affairs is to be promoted rather than resisted. This will also be the case according to much of the bioethical literature. To take one central (but also much criticised) example: according to bioethicist John Harris, choice will be sufficiently autonomous when not restricted by

"(1) defects in the individual's ability to control either her desires or her actions or both;
(2) defects in the individual's reasoning;
(3) defects in the information available to the individual, upon which she bases her choice;
(4) defects in the stability of the individual's own desires" (Harris 1985)

Hence, autonomous choice consists in drawing the correct inferences from the correct factual premises under conditions free from undue influences and social pressures. Here, the conception of autonomy is directly linked to the actors' possession of correct scientific knowledge. Although less rigid, similar conclusions can be drawn from Beauchamp and Childress, by whom autonomy is defined as action in "accordance with a self-chosen plan, analogous to the way an independent government manages its territories and sets its policies". This action, furthermore, should be allowed carried out free from "interference by others and from limitations, such as inadequate understanding" (Beauchamp and Childress 2001:58). Beauchamp and Childress do not connect the notion of autonomy directly to scientific information, as does John Harris. To show respect for autonomy, they say, may also entail the negative obligation to respect individuals' choices when they are *wrong* about the situation at hand. However, there also exists a *positive* obligation: "Respect for autonomy obligates professionals in health care and research involving human subjects to disclose information, to probe for and ensure understanding and voluntariness, and to foster adequate decision-making" (*ibid*., 64).

Hence, on this account, the main task of health care workers, lawyers and bioethicists alike will be that of creating and fostering a *space of autonomous decision-making* in which the individual is to be left more or less to him or herself. It is a space that, once created, is to be protected but not interfered with. I will have something more to say about spaces of decision-

making and their relation to time for decision making in the following section. As should be clear by now I do not think we should be satisfied with the above version of good decision making. I take it to be abstract and negligent of the wider context of choice. In the worst case scenario it will not foster autonomous choice and it may even take on a coercive character.

Let me briefly recapture some arguments from previous chapters.

First of all, I have underlined the transfer of risk responsibility that accompanies the therapeutic gap. Because therapies are lagging behind the ability to diagnose, responsibility for health is transposed from the health care system to the individual patient, supposed to turn his or her genetic profile into a rational planning project. This character and tendency of genomic medicine, fitting well into the fold of preventive medicine, will make itself increasingly marked with the projected expansion from genetics to genomics.

As therapeutic objects are scarce, more comes to hinge upon *information* as such. Proponents of genomic medicine, such as (Bell 1998; Khoury 2000; Guttmacher and Collins 2003), argue that the genomic era is already upon us, and that we better start transforming the health care system rapidly in order to adapt to the developments propelled forward by the Human Genome Project (and other projects succeeding it). However, even these authors recognise the decisive discrepancy and time-lags between genomic researchers and the knowledge and understanding of health-care workers, a problem they seek to overcome by rapid and large scale re-education of medical doctors and other health care workers as well as the general population. I have quoted research (in this chapter) showing how medical doctors already have problems coming to terms with statistics, risk analysis and communication within the present state of knowledge in preventive medicine. Can we realistically expect a fast up-grade of genetic and statistical literacy among health care workers? Do we know that such a transformation will be in accordance with the everyday concerns and problems of most health care workers? And how would this be accommodated and adapted to demands within other important fields of medicine, simultaneously demanding from medical doctors that they be up-to date on the latest information? (Strand and Schei 2001).

And if we should also include the wider population of possible patients, it should be clear that the above mentioned problems, restricted to the organisation of the health care system, are

only the top of the ice-berg. For how do you turn whole populations into genetically informed decision-makers?

Overwhelmed by complexity?

Articles promoting genomic medicine on a general basis, like (Burke 2002) and (Guttmacher and Collins 2002), will often contain a last section on social and legal consequences in which the importance of informed consent is forwarded as a means of caring for both social consequences and the autonomy of the patient. However, as argued above, these visions of health care tend to regard scientific developments and technology transfer in terms that appear simplified from the perspectives of the social and humanistic disciplines, not to say from the perspectives of health care workers or from patients' point of view. It is a top-down perspective in which the many complexities of the clinical encounter, social and cultural developments and the life-worlds of the patients are projected in accordance with a linear vision of technology transfer and clinical utility. From the perspective laid down in this project, the following account, given by Onora O'Neill, may be more adequate and up to the actual situation:

> "…problems arise…not because most members of the public have limited understanding of science, nor because most scientists are poor communicators, but rather because the matters to which consent are sought are more numerous and more complex, and sometimes rendered increasingly opaque by the very structures of accountability that are supposed to protect the public. Even those with a high level of scientific training and culture are challenged by the ways in which information is now organised. The answer to this problem cannot be to provide more information, more regulation and more fine print: there is often all too much information provided, and more fine print around than anyone has time to deal with" (O'Neill 2001).

We may envision overwhelming complexities on two sides: that of the health care system and that of the life-world of the patient. On the side of the health care system, a cadre of medical doctors, scientists and health personnel have replaced the model of the intimate face-to-face encounter of patient and physician. It is this state of affairs that is captured in the title of David Rothman's book *Strangers at the Bedside* (Rothman 1991), and which has been described as the expansion of the health care system earlier in this chapter. When treated by a number of different specialists and health care workers: To whom should consent be given? In the opinion of O'Neill, the entrance of heavy information technologies coupled to genetics into medicine is *accelerating* this tendency:

"We have left behind a world of I-thou doctor-patient relationships, and now inhabit one in which the individual patient and the individual doctor draw many others into complex forms of connection. In medicine, as in many other parts of life, we constantly deal with many-many relationships. Nowhere are the implications of this basic and uncontroversial fact about contemporary medicine stronger than in those parts of life in which genetic data are collected, stored, used and disclosed" (O'Neill 2001)

To grasp the meaning of this quote, it may be useful to return to Francis Collins' vision of the $1000 genome. Within that vision, genetic knowledge is deployed to establish the genetic profile of the single patient in order to individualise treatment and drug therapy. Even though we grant the many positive effects this could have, regulatory challenges will be great. In short, problems are likely to aggregate as even more people, more professions and more procedures to safeguard the privacy of the patient will get involved. It will not be sufficient that the patient consents to the taking of his or her genetic profile to one single doctor. A genuine informed approval will also entail that the patient consents to the institutional rules laid down to protect his or her privacy, i.e. rules about data access and protection. The amount of information required for informed consent is drastically expanded, no longer dealing with the exchange of information between physician and patient, but should also be taken to include consent to the rules and procedures for data protection. The importance of this is underlined by the interests that third parties, such as police, insurance, government and employers may take in the same information (*ibid.*). Concerning institutional rules for safeguarding information, however, Beauchamp and Childress admits that patient autonomy may yield to competing interests:

"We should evaluate institutional rules not only in terms of respect for autonomy but also in terms of probable consequences of imposing burdensome requirements on institutions and on professionals. Policies may legitimately account for what is fair and reasonable to require of health care professionals and researchers, the effect of alternative consent requirements on efficiency and effectiveness in delivering health care and advancing science, and the effect of consent requirements on the welfare of patients. Nevertheless, we take it as axiomatic that *the model of autonomous choice*…ought to serve as the benchmark for the moral adequacy of institutional rules" (Beauchamp and Childress 2001:79).

This last reservation, however, will be rendered close to meaningless in a situation in which the context has changed radically:

"Genetic information on this scale would be held on a smart card or in a central database. Any hope that such information was private would have to depend less on professional codes governing the action of individual doctors and more on intricate regimes of data protection. Any thought that individuals could determine how such information should be held and used would prove implausible if the complexity of the information exceed what individuals can grasp or interpret. Any thought that

individuals could understand their genetic profiles and decide just which data they would disclose to which others or for which uses looks implausibly demanding" (O'Neill 2001)

If we are to follow the recommendations of Beauchamp and Childress in this matter, we end up close to absurdity: the autonomy of the person may be overridden by the greater interest of growth in science and health care. But as far as possible we should also attend to and observe the autonomy of the individual, which should, in the last resort, serve as the blueprint for institutional rules. Both these arguments, however, are close to senseless given the demands placed on the informed consent of the patient in the face of increasing information. The autonomy part of the argument, intended to balance the interests of the system will, in effect, be cancelled out from the very beginning by the shear amount of information:

"From the point of view of individuals who are working out whether to give or withhold informed consent, complex regulatory systems can look more like another hurdle than a safeguard. The difficulties will grow as genetic data become more and more readily available, and as the construction of electronic databases combining genetic, medical and other information becomes more and more feasible. Individuals could not be expected to develop an adequate grasp of their own genetic information, or to give any but the most general, -that is, minimally informed –consent to the collection, storage, uses or disclosure of parts of that information" (*ibid*.).

In that case, what remains is the institutional perspective, and we will be back to the situation attacked by Hans Jonas and the early bioethicists in which the interests of "the concrete individual" is sacrificed to those of abstract systems of action and knowledge.

These may be imagined scenarios, projections of a possible future. But this future may not be distant. Here is how two patients interviewed about decision making during cancer treatment experienced the decision to undergo genetic testing:

"The 2 patients who were offered a test during medical treatment had a sense of being part of an unstoppable chain of medical processes. Metaphorically on a conveyor belt, they experienced the test decision as submerged in a context of numerous other interventions. By the time of interview both of these interviewees felt that they had never actively *decided* to have a test" (Scully, Porz et al. Forthcoming)

Research on consent to use of genetic material in biobanks may also confirm the description given by O'Neill: in many cases, the donors do not know to what it is that they have consented (Hoeyer 2003). In a survey of donors to a french biobank, Ducournau and Strand found that many (about 1/3) simply chose to delegate responsibility to researchers and administrators of the projects, thus investing these actors with a "natural trust". Others (ca. ¼)

signed the consent form while openly distrustful of scientists, for instance in order "not to leave the matters to scientists alone", whereas about 1/3 consented in the way more or less intended by legislators (Ducournau and Strand Forthcoming).

The parallel to consent in biobanking may tell us something about the ability or the willingness of lay persons to perceive complex scientific information. However, the difference is also great, as the context in which consent is given is drastically altered for the patient undergoing genetic diagnosis. As noted by (Hofmann 2006), in genetic diagnosis the risk situation is radically altered: whereas participation in biobanking may be said to constitute almost no risk at all, the repercussions of a genetic diagnosis may be grave, and so serious emotional pressure will alter the planning capabilities as well as the cognitive functioning of the patient. As frequently argued, illness and disease are exactly those states in which we are *not* autonomous, at least not in the sense ordinarily intended in models of rational choice:

"…to suffer or to be in pain is to lose one's full sense of self. We cannot function normally as individuals when we are sick, and thus our ability to be a self is compromised. Medicine must be committed to restoring that integrity, or at least protecting it, when the patient is clearly unable to make decisions" (Tauber 2000:67).

In an excellent study on patient's experiences with genetic testing, Scully, Porz and Rehmann-Sutter found that many patients under severe emotional pressure actively choose to split decision-making into manageable parts, or "microdecisions". This was especially so with women undergoing prenatal diagnosis, as these patients had to decide much faster than other patients (for instance those undergoing predictive testing for Huntington's). Facing possibly very hard decisions following diagnosis, many said they "mentally excluded this knowledge when thinking about the test, restricting their focus of attention to the immediate weeks or even days ahead". According to the authors, however, this should not be perceived as a letting go of agency:

"To preserve moral competence, they chose not to draw on some information they had…Our interpretation suggests that a situation where a woman has agreed to testing without seemingly thinking about the consequent possibility of termination, is not necessarily irrational, nor due to errors of comprehension or communication, but might in fact be necessary for her moral agency" (Scully, Porz et al. Forthcoming).

If it is the case that patients actually manipulate the field and the time of decisionmaking in accordance with their own preferences (their life-world), bioethical accounts of autonomy and informed consent, while not being altogether wrong, may still be missing central aspects of moral agency. Information processing does not take place according to definite rules, as for instance referred in the above quote from (Harris 1985).

Concluding. The socio-material contract revisited

In this section, I have given reasons why the notions of autonomy and informed consent, when uncritically applied to genetic/genomic medicine may end up by seriously misconstruing moral agency as well as the context within which that agency is supposed to be carried out, i.e. the clinical encounter. Before that, I also argued that the socio-political context as well as technological possibilities has also been seriously altered, so that medical risk is increasingly transferred, from the medical system to the individual patient (this argument is strengthened by its convergence with Beck's theory of individualisation). The strong emphasis upon autonomy and individual choice is likely to strengthen this tendency rather than alleviate it. This may sound like harsh criticism, and obviously many will disagree, bioethicists as well as others. However, it is also quite remarkable how much of this criticism is constantly repeated by central actors within bioethics itself. Some of these criticisms have been alluded to above in quotes from Albert Jonsen, Onora O'Neill and others.

Robert Veach, while acknowledging the important historical role of informed consent, ascribes to the concept a transitory status only: "Consent may be what can be called a transition concept, one that appears on the scene as an apparently progressive innovation, but after a period of experience turns out to be only useful as a transition to a more thoroughly revisionary conceptual framework" (Veach 1995). In the face of growing complexity, social as well as scientific and technological, the exclusive emphasis upon autonomy and informed consent has come to make up what Daniel Callahan terms "ethical reductionism". The main target of criticism is the "principlism" forwarded in Beauchamp and Childress' *Principles of Biomedical Ethics*:

> "The reductionist drive of principlism has had some debilitating effects on the field. One of them has been to make ethical analysis easier than it actually is, offering a kind of handy shortcut to the making of decisions (which may also explain its attraction to busy physicians who are looking for more simplicity, not more complexity, in their clinical lives)…At its worst, ethical reductionism dotes on the language of rights, wants clean and uncluttered principles, and flees from pressing larger questions of the relationship between medical possibilities and long-range human welfare, matters thought best dealt with (if they cannot be avoided) procedurally rather than substantively" (Callahan 1999).

How did this come about? How could the initially legitimate role of bioethics be transformed from a socially conscientious and politically relevant movement to a discipline in which most of the pressing social, political and ethical issues are substituted for principlism?

Presuming that the question is accepted in the first place there may still be many and various answers, perspectives, and, guaranteed, many further questions. We must, however, return to some of the premises laid down in this project, and try and make sense of it from that perspective.

If we observe the common trajectory of autonomy and informed consent we notice how they so to speak issued in the laboratory, addressing the problem of research on humans. From there, it grew to encompass also other contexts, significantly that of the clinical encounter. By including more groups and individuals in the decision making process a more socially robust form of knowledge production was sought out. Significantly, resources from philosophy and political theory were deployed in order to come up with alternative bases of decision making. But it could also be argued that the discourse never really left the laboratory.

In chapter 3 I described how the socio-material contract was constituted at the base of the modern production of knowledge and organisation of action. According to that agreement, the natural order was to be represented to science whereas the social order was to be represented by politics. However, describing the situation as a mere out-differentiation of qualitatively different domains only reveals part of the story. As described in the section "Two anthropologies", the mechanistic notion of the universe came to set its definite marks also on the ethical, later also political, domain. Within the Cartesian world-view, ethics is what's left (i.e. freedom) after the scientific has spoken: first, establish the facts of the matter, then decide how to use that knowledge in the most useful manner (Taylor 1989). In this way, the scientific came to set its definite mark upon the language of ethics and politics. Says Stephen Toulmin:

"From the mid-seventeenth century on…an imbalance began to develop. Certain methods of inquiry and subjects were seen as philosophically serious or "rational" in a way that others were not. As a result, authority came to attach particularly to scientific and technical inquiries that put those methods to use. Instead of a free-for-all of ideas and speculations - a competition for attention across all realms of inquiry – there was a hierarchy of prestige, so that investigations and activities were ordered with an eye to certain intellectual demands. Beside the *rationality* of astronomy and geometry, the *reasonableness* of narratives came to seem a soft-centered notion, lacking a solid basis in

philosophical theory, let alone substantive scientific support. Issues of formal consistency and deductive proof thus came to have a special prestige, and achieved a kind of *certainty* that other kinds of opinions could never claim" (Toulmin 2003:15).

The issue alluded to by Toulmin has been noted over and over again during this project: formal ways of reasoning came to set their definite marks also upon ethics and political thought, domains traditionally dealing with social action in non-formal ways more in accordance with the ways in which action and agency are normally perceived, what Aristotle termed *practical reasoning*. The supreme discipline of practical reasoning, Aristotle held, is *politics*. Politics deals with what is good and desirable in life, and so cannot be but a partial, inconclusive and in-exact science:

"…in discussing subjects, and arguing from evidence, we must be satisfied with a broad outline of the truth; that is, in arguing about what is for the most part so from premises which are for the most part true we must be content to draw conclusions that are similarly qualified…it is a mark of the trained mind never to expect more precision in the treatment of any subject than the nature of that subject permits; for demanding logical demonstrations from a teacher of rethorics is clearly about as reasonable as accepting mere plausibility from a mathematician" (Aristotle 1955:Book One).

To remain in philosophy a little longer: in Kant's account of theoretical and practical reason, the two domains of science and ethics are sharply separated. However, theoretical and scientific reasoning had already set their definite marks upon ethics, upon politics and law. The benchmark of correct action and moral agency is no longer situated within any conception of the substantially good, but is rather conceived of in terms of universal rationality, i.e. the categorical imperative. In Kant, then, we end up with a notion of moral agency and morally good action which is precisely as emptied of content as it is universal (Wellmer 1986).

But the theories of philosophers were, of course, only articulations of what simultaneously took place in society itself, more concretely in the formation of scientific disciplines and professional systems of action (Parsons 1954). As described by Toulmin: "The seeming certainty of Galileo's mathematical methods had a natural appeal, and they soon took hold. In theory and practice alike – philosophy and jurisprudence, as much as the training of infantry – Skill gave way to Technique, Artisanry to Artisanship" (Toulmin 2003:32). This gradual replacement of the basis for action, from art to science, also makes up a central part of Beck's theory of reflexive modernisation, which I see as a central point of convergence between Beck's theory and hermeneutics. It has also been noted in the partial exposition of the

development of medicine: the introduction of the counterfactual organiser as a way for dealing with increasingly more and more cases according to the same rationally and experimentally established principles of action. Along with the gradual expansion of the medical system, it sees, corresponding notions of universality are imported from politics and philosophy in order to regulate developments.

After a period of initial social engagement and political attention to the issues raised by bioethics, not the least triggered by the political and social movements of the 1960s and 1970s in which a reference point independent of the language of science and technology was sought out, the discipline has more or less returned to "ethics as normal". This may not constitute much of an historical, or even sociological "explanation" of the present shortcoming of bioethics, but it does, I think, say something significant about the sources of legitimacy upon which we call in times of uncertainty. Within this understanding, it may come as no big surprise that the rational agent, autonomy, is called upon in order to regulate the fast-expanding fields of genetics and genomics.

For the notion of rational agency does indeed reside at the very core of the modern project. Not only as a philosophical ideal, but also very much as social and cultural ideal. If it was not for the scientific project, the notion of rational agency would no doubt look very different. As the socio-material contract was established, the rational observer and decision-maker travelled from the laboratory and into society at large: he was efficiently socialised under conditions of great social and political strife and uncertainty as a neutral mediator between incompatible notions of natural and social order, as found within scholasticism of the 17th century or within revelatory or natural religion. Historically speaking, the scientific world view was early on exported, from the laboratory and to the wider social context, in the Royal Society in London (Shapin 1999). One central mediator was John Locke, one of the main architects behind the notions of liberal democracy.

Indeed, the autonomous actor may very well have arisen in the laboratoty itself, then as the impartial observer of scientific experimentation. Locke himself, both a medical doctor and a political scientist, drew many of his thoughts from central experimentalists and natural philosophers such as Robert Boyle and Isaac Newton. With the reservation that Locke himself did not use the word autonomy, but rather rational self-governance or the like, we may still accept the following description given by Alfred Tauber:

"A self-consciousness among scientists of the period grew from a concern about how our perceptions determine our knowledge of the world and how our minds influence our perceptions. These early scientists well appreciated that rationality (our cognitive functions) and empiricism (our perceptual faculties) are interwoven in such ways that separating the two is impossible. As much as one might want to perceive the world objectively with no projection of prejudice or subjectivity, it is literally impossible to do so. At the same time, it became clear that description and experimentation demand just such a divorce, because the scientific method was ostensibly based on a scrupulous objectivity in which the observer would simply report his data and draw the logical inferences. Thus observer-autonomy was a key precept of the nascent scientific method, and philosophers struggled to establish the basis on which claims of objective knowledge could be made…The problem of autonomy migrated from the laboratory to the political arena and became central to Locke's philosophy. Throughout the Enlightenment philosophers continued to wrestle with with both the implications and the philosophical basis of his position, which pervaded both the judicial and the scientific discussion of this period. For Locke the political theorist, autonomy served as a crucial, one could say *the* crucial fulcrum for a society struggling to transform itself from the subject of the divine rule of monarchs to self-government ruled by the democratic rights of the individual, seen as both the sole agent of his pursuit of happiness and arbiter of the social will" (Tauber 2000:30).

This may indeed have been the main reasons why the socio-material contract emerged at the core of the social and political debate of the 17th century, namely its ability to ascribe cognitive as well as social functions to different domains of knowing and acting, and at the same time remaining within a relatively unified notion of the natural and political order, one that was mainly founded in the scientific project. This analysis is also confirmed by recourse to Charles Taylor well-known analysis of the sources of the modern self:

"what probably made Locke the great teacher of the Enlightenment was his combination of these two factors: that he offered a plausible account of the new sciences as valid knowledge, intertwined with a theory of rational control of the self; and that he brought the two together under the ideal of rational self responsibility" (Taylor 1989:174).

With these historical and philosophical reflections in mind, we may cast a new glance upon the dilemmas of bioethics. The necessity of establishing bioethics as a discipline with its own methods and in relative independence from the methods of scientific reasoning was noted by many of its early proponents. Indeed, to get in the position to be able to communicate with scientists, medical doctors and patients alike, it was necessary to re-establish philosophy as a practical and public discipline, far removed from the abstract and indeed anti-social meta-ethics of the day (Jonsen 1998). We may reiterate an earlier quote from Daniel Callahan: An ethical decision will not be satisfactory to the person whose decision it is unless it is compatible with the way in which the person ordinarily thinks about himself and what he

takes his life to be" (Callahan 1973). And, in a well known article, Stephen Toulmin wrote that

> "By reintroducing into the ethical debate the vexed topics raised by particular cases, they [bioethicists] have obliged philosophers to address once again the Aristotelian problems of practical reasoning, which had been on the sidelines for too long. In this sense, we may indeed say that, during the last 20 years, medicine has 'saved the life of ethics', and that it has given back to ethics a seriousness and human relevance which it had seemed – at least, in the writings of the interwar years, to have lost for good" (Toulmin 1982)

And, in the words of Albert Jonsen, thanks to bioethics, "The spirits of the antique casuists inhabit the modern hospitals" (Jonsen 1986). But, as seen in the discussion on informed consent, and, as argued by Daniel Callahan, "principlism" has substituted this basically practical and judgement-based way of reasoning for a set of ready-made principles, significantly that of autonomy. One reason for this, then, should be seen as residing in the "fact" that the practical sciences, like politics, ethics and jurisprudence, never really wrestled themselves free of the influences from the natural sciences (cf. earlier discussion of methodological dualism). It seems that is it indeed very hard to secure a relatively independent position outside of the world-views of these sciences. Another reason, which I would like to explore in the following, is of a more sociological kind. Under conditions of "intensified modernity", such as constituted in and by the Human Genome Project, the speed with which new technologies are introduced becomes so high that the decision making becomes almost compulsory (Beck and Bonss 2001). In times of greater uncertainty, it seems, we come to rely upon ever-more simple principles of decision making. But this is exactly one of the reasons why we the second modern production and distribution of knowledge comes to result in ever more non-intended side-effects: "Handlungen haben genau dann *nicht intendierte Nebenfolgen*…wenn unser Wissen bezüglich einer der gennanten Faktoren der Entscheidungssituation unvollständig ist" (Sellmaier 2004).

One significant factor in promoting this state of affairs is the strengthened role of the economy in the new production of knowledge (Nowotny, Scott et al. 2001). Although not visible at first sight, this state of affairs can also be led back to early modernity and the enlightenment.

While not wishing to forward the absurd notion that the theories of liberal philosophers were directly translated into action, they most certainly went well along with, and articulated many of the central concerns, operating in the formation of modern society. As such, the renewed sense of mastery and control gained through the scientific method was fast transported into hospitals, the military system, schools and the bureaucracy (Taylor 1989; Toulmin 2003) (these developments have also made up the particular focus of many of Foucault's analyses). In Locke's philosophy we also find the preamble to and an early legitimation of the modern political economy, and also this was grounded in the notion of the rational self, which was intimately connected to the right of *property*. Because man has the property in his own body, and because he transforms nature through his bodily *labour*, he also establishes his right to the products of nature as refined by him (Locke 1966). Through the notions of labour and property, Locke refined the social contract as initially articulated by Hobbes (cf. chapter on methodology). In Hobbes philosophy, the sovereign was instigated as the sole poitical authority in order to avoid the tumultuous state of nature in which everybody stood up against everybody. In the philosophy of Locke, however, sovereignty is transformed and redistributed: from the single sovereign at the top of the political system and to the single individuals, now to be regarded as self-governing ("autonomous") agents. By consenting to the social contract, men agree to come together under the rule of law in order to protect the results of their labour, i.e. property. The protection of property, therefore, is the prime, and for many liberalists, *sole* legitimate task of the state. Justice consists in nothing but the protection of the individual's property, a notion that has been revoked in more recent times by Robert Nozick. It is, says, Locke, the notion of labour that introduces *value* into the world: by refining nature we also become capable of *storing up*, of accumulating. Hence, the labourer creates surplus value for society, which may next be exchanged for other goods or for the universal medium of money (Manent 1995). The common interest of men, and the basis of the social contract, becomes that of securing the just and fair exchange of goods and money. Hence, rather than having the sovereign at the top of the political system, the state is now instigated in order to protect the legitimate and rational interests of man: the working of nature and the accumulation of wealth. Rather than fight amongst themselves, citizens now turn towards nature as their primary object of action. Hence, we get an early identification of two domains supposed to be *neutral*, hence also sufficient for establishing a common ground for acting and thinking. Those two domains are science and the economy:

"The same movement that brings the sovereign state to forbid men to exercise personal power over each other is going to lead the members of society to turn progressively away from each other, to avoid the encounters in which they experience mortal dangers. They are going to seek a neutral ground for their actions, one where they do not meet upon their fellow men and where they do not encroach upon sovereignty. Up to the constitution of the sovereign state, the primary object of each person's action was the other man. Henceforth, that object will be *nature*. Men turn away from men and in stead turn themselves towards nature so as to understand and control it. Science is neutral and its conclusions are imposed on everyone. It is above the particular interests and partisan passions of men, not unlike the sovereign, at least in principle. The economy, closely linked with science, tends to become the arena par excellence of human activity because, in its finality, the economy is directed towards nature and not towards other men. The development of absolute sovereignty within the framework of civil society, have the same motivating force" (Manent 1995:47).

Hence, we see that the call for the rational agent is deeply rooted in western culture; he is indeed pervading all the domains of science, economy, politics and ethics. He is also likely to be called upon in order to serve the interests of all of these domains.

As noted in an earlier chapter (referring to Heidegger), both technology and economy share the common propensity of a "storing up", of resources and of values. Referring to Locke, we also see how science and the economy found themselves at the centre of the establishment of the modern order. We should, therefore, not be too surprised when the two, in late modernity, come to intertwine in new and more powerful ways through the shared medium of technological development. Technology, it seems, comes to constitute the connecting medium between the hidden hand of the market and the hidden principle of nature, in the case of medical genetics that of physiological function.

The "rationalisations of rationalisation" represented through the intrusion of ethics and the economy into the biomedical sciences could thus be regarded as the realisation of the modern project. As such, it may seem that the three principles of the central dogma, patentability and autonomy may indeed enter into a greater unity promoting health and wealth for all. However, these are principles, concepts residing at the top of very complex practices. In each of the three cases, it seems, as says Beck, increasing gaps between concept and reality, between simplicity and complexity. The counterfactual organisers of the central dogma and autonomy seem to become increasingly abstract as they are turned into information by technological developments, and, at the same time, increasingly invested with speed and demands for fast decisions as they become deeper entwined in an accelerating globalised knowledge economy. At the same time, these counterfactual organisers do, in some sense or other, refer to real objects in the world: in terms of the biomedical researcher, the central dogma refers to the

genome as the basic principle of physiological function. For the investor, the different parts of the genome are more likely to be perceived in terms of commodities, as such part of the ups and downs of the global economy rather than essential parts of physiological function. And, for the clinician on his side, genomic information may be but one among many competing theories of causal explanations invoked in order to promote the health of the ultimate object of attention: the patient. The patient is of course also a *subject*, worthy of respect and autonomy; but he may, however, also be conceived of as a consumer by the pharmaceutical industry.

"Wie durch eine Brennglas", say Ulrich Beck and Stefan May, "bündeln sich die neuen gesellschaftlichen Probleme in der Entwicklung der medizinischen genetik"(Beck and May 2001). One way to understand this quote would be this: genomics, if realised, would pose an ultimate realisation of the modern project *if* the many spheres of knowing and acting would come to constitute a higher unity promoting all of the above mentioned goods. With recourse to the notion of counterfactuality a central asset of the project is attempted highlighted: most of its rewards lay in the future, but it is demanded of us that we act upon the possibility of many rationalities coming together, a massive co-production of social and scientific order, *now*, if the potentialities of the project are to be realised. Such a co-production ultimately hinges upon the realisation of the genome as a successful technology. It also hinges upon this technology not becoming more cost-demanding than being capable of offering technology and health *for all*, or at least those capable of paying up with $1000, or those finding themselves within a welfare system willing and capable of paying for their genetic profiling.

Presupposing that this is realised, the state and its welfare system will have to compete with industry and commerce about the property rights and, ultimately, the cost-efficiency of the genome project, proteomics and the like. This may be a tough call, also for industry, insofar as it will have to readjust: from standardised and industrialised mass-production, to tailor-made and individualised pharmaceutical products. In the absence of these visions coming through across a broad scale (individualised medicine becoming a possibility for the rich only), much of the responsibility will end up where it seems to be heading at the moment: with the individual patient or citizen. In that case, the genome project will have issued in a perversion, rather than a promotion of, the Enlightenment project: to enrich society through empowering the individual.

Concluding projections

more time for leisure
more time for pleasure
more time for education
more time for recreation
more time to contemplate
more time to ruminate
more time
we need
more time

Linton Kwesi Johnson, *More time*

From the previous analysis it appears that the Genome Project is really, in Beck's terms, the embodiment of "the modernisation of modernisation": from within the confusingly complex meeting of rationalities of science, technology, economy and politics it appears that some very old and, at the same time, very *modern* sources of knowing, acting and producing are coming together within new and sharpened configurations: The rational agent, the accumulation of wealth, science as the rational exploitation of the neutral domain of nature (the notion of *hyper*-modernity springs to mind).

If that is the case, and bearing in mind Heidegger's notion of science as technology, the question also announces itself: did I really appropriate Heidegger, or was I appropriated by Heidegger? Is modernity basically *Gestell* after all?

Luckily, I do not think the question needs answering. However, it seems that although we (rightly) may criticise Heidegger for his ignorance of the social dimension, his philosophy of technology still has something going for it. We also saw how, in the chapter on Heidegger, his philosophy of technology does not imply determinism, but that it may easily be interpreted as doing so. Nevertheless: In applying a derivative and sociologised version of Heidegger to the production of the genome, the role of politics and the economy in promoting science and technology was also highlighted: the acceleration and up-grading of research in the 1980s were not simply a question of technological development, i.e. recombinant DNA as a properly useful deployment of genetics; it was also a matter of a *willed* political intervention in the face of changes in industrial production and economic situation.

For Heidegger, living with technology is *not* simply a matter of (rational) choice, but rather a real-time *happening*. As briefly discussed in the section of trust: within this happening a number of attitudes are possible towards technological developments, also that of an active and autonomous stance. Still, whether one finds oneself passively at the mercy of technology or is able to deploy it actively, will depend strongly upon the context, socially, politically, culturally, physically, in which one finds oneself.

Still, it seems, people (patients) may increasingly find themselves in situations in which they will have to choose, autonomously or not. *Individualisation* is not, in that respect, chosen by people in general, it is more a consequence of deeper changes within the structures of knowing, producing, working and acting, what Beck terms *Strukturwandel*. Therefore, although we accept the necessary expansion of the analytic framework also to include economy and politics, the determining forces are very strong. Indeed, from the present analysis it may even seem that it is exactly the coupling of science *through* technology to the economy which may produce impressions of determinism, i.e. a development that is not really *chosen* in the democratic sense of the term. This, I take it, is also an important reason why theories of deliberative democracy and justice should be handled with some care in analyses of science and technology: in focusing exclusively upon the political and deliberative dimension they may run the risk of covering up a whole spectre of *happenings* taking place before politics or ethics have their say.

It emerges that the rationalisation of rationalisation may take on at least two different meanings: first, it may mean the intensification of modernity's forces under the aegis of ever-more rationalising, ever-more wealth-maximising modes of producing and organising (Beck and Bonss 2001). This should come as no surprise, as the instigation of the socio-material contract had the character of ascribing many of the same values and ideals of rationality among different actors and domains of action. Within hyper-modernity, what has previously been separated seems to be pulled tighter together: science, technology, economy and the rights of the individual. We have seen how science and the economy meet through ever-stronger technologies, and how bioethics, in spite of its initial success, constantly runs the risk of being drawn into the fold of science and technology. Second, the "rationalisation of rationalisation" may be taken to mean the introduction of alternative modes of knowing, producing and organising, coming to the fore as the integrating forces of modernity come to

yield non-intended side-effects to the social order, one consequence of which may be the deterioration of trust in expert knowledge, in science and in the medical profession.

The new ways of knowing and producing represented by genomics as a hyper-modern mode of knowledge production, generates and re-distributes forms of knowledge, economical resources and technological know-how on the hands of exclusive groups: scientists, corporations, universities, and research centres. To a large extent, these are the groups that make development happen, whereas to most others, development simply happens. I have tried to describe this difference by frequent allusions to the *time* in which developments take place. The intertwining of science, technology and economy undoubtedly speed up developments to an unprecedented pace. This is not unproblematic: the time required to make a business transaction is not the time that it takes for a physician to make a diagnosis, not to say conceive of a good treatment. And the speed with which new diagnostic technologies are introduced to the market or to the health care system is not the time it takes for a patient to come to terms with a devastating diagnosis:

> "Faster testing is generally seen as benefiting both patient and the healthcare provider. But we might need to bear in mind that just because the test results come faster does not mean that the information they provide has also become trivial or more easily absorbed by patients…it may also be that a longer testing process offers unexpected benefits in giving extra time, not solely for rational consideration of the issues, but to safeguard their agential capacity…As the mechanisms of testing speed up, time for reflection may have to be built into the test process artificially" (Scully, Porz et al. Forthcoming).

In finishing off I would like to expand and generalise this point to the general production and distribution of knowledge: slowness, reflection and understanding will have to be built into the generation of new knowledges if they are going to retain their social and cultural legitimacy. For this we will have to deploy a wider range of sources than those mainly considered at the present.

When we are to assess the broader value of technological development to the promotion of health care, we should ask: is it articulated in a language that is capable of addressing the central concerns of the most important actors involved in the negotiation of health promotion? This should mean that it must be able to address: 1) patients and patient's organisations, 2) medical doctors in general (not just medical geneticists) 3) health care workers in general, 4) the legal profession and policy makers, and 5) other groups, centrally future generations.

But language is not an isolated matter. It is situated in bodily action. *Social* action is also situated in institutions. Thus, we need institutions in which a sufficiently "thick" understanding and articulation of social, cultural and bodily action can be embedded, what Roger Strand has termed "thick complexity" (Strand 2002). We need institutions that can bring a wider range of cultural sources into the production and distribution of new, knowledge-based practices. The negative alternatives entail institutions incapable of handling anything but "information", "innovation" and "novelty".

If we take it that technological development, when seen from a broader social perspective, has more the character of a happening than something that is autonomously chosen, it also emerges that adapting to technological change is not simply a matter of finding the correct political or ethical procedures. As put forward by both Beck and Heidegger, it is more a question of finding ways of living with and coming to terms with technology (Heidegger 1977; Heidegger 1978b; Beck 1993). I am not going to try and enumerate all the things that would have to happen for such a process to come about. However, as academics, we should try and project other ways of producing knowledge. In order to develop sufficiently "thick" institutions we will have to bridge the gap between the two cultures of science and culture. At the present, it seems that we are producing technical competence and capability but without sufficient accompanying understanding of that very knowledge. Many things may be seen as standing in the way of improved understanding: first, a general ignorance of questions concerning science and technology on the side of the humanities, but also of the social sciences. Second, a nearby total lack of reflection upon the social consequences of science, and of the historicity of the single disciplines within the science curricula. Third: deeply ingrained habits of thought, promoting science and technology as neutral and culture and society as rest-categories that, in cases of importance, are allowed to have their say only after the scientific has spoken. *Ethics* cannot by itself bridge this gap, as its sources remain too dependent upon notions of agency taken from the experimental sciences, frequently exported through economics and organisations theory. Let us (again) turn to the diagnosis of C.P. Snow, this time as reconstructed by Steve Fuller:

"Although Snow himself supposed that the two cultures suffered from *mutual* incomprehension, his speech clearly left humanists with the impression that the burden was primarily theirs…However, Snow was making a much more even-handed point, namely, that while scientific skills are singularily necessary for the survival of humanity, scientific training fails to instruct the moral imagination, especially the facility with alternative futures that is typically developed by the humanities. Snow's

ideal civil servant would thus be equipped with a humanist's sense of ends and a scientist's sense of means" (Fuller 2000:325-26).

Hence, we should put our energy and resources into imagining new inter-disciplines for future research administrators, politicians of research as well as researchers and educators themselves. The purpose of this would be to establish new and better regulatory bodies aiming at more sustainable and socially viable production and distribution of knowledge.

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