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Sustainable and responsible preventive medicine

Conceptualising ethical dilemmas arising from clinical implementation of advancing medical technology

Doctoral thesis
for the degree of philosophiae doctor

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Faculty of Medicine
Department of Public Health and General Practice

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“Du skal skrive ditt fag”

Per Fugelli

To Iðunn and Jan

TABLE OF CONTENTS

	page
ABSTRACT	**9**
PREFACE AND ACKNOWLEDGEMENTS	**12**
1 INTRODUCTION	**17**
1.1 Outline of this thesis	17
1.2 Voices of concern	21
1.3 Definition and goals of medicine	24
1.3.1 Curative versus predictive and preventive medicine	25
1.3.2 Discourse on medical risk	26
2 THEORETICAL PERSPECTIVES	**30**
2.1 Conceptualising health	30
2.1.1 The Goals of medicine project's health definition	31
2.1.2 Antonovsky's model of salutogenesis	32
2.1.3 Van Hooft's framework on subjectivity and health	34
2.1.4 Situatedness, embodiment and health	36
2.1.5 The health benefits of a narrative	41
2.2 The nature of medical knowledge and 'evidence'	43
2.2.1 Mainstream biomedical research	43
2.2.2 Is medical progress stagnating?	45
2.2.3 The biomedical disease model and its limitations	47
2.2.4 How medical doctors think – reflections by McWhinney and Cassell	48
2.2.5 Call for new approaches: complexity science and syndemiology	50
2.2.6 Objectivity critique and the patient-centred clinical method	51
2.2.7 Evidence-based medicine	57
2.3 Conceptualising medical ethics	63
2.3.1 Principlistic American bioethics and its shortcomings	64
2.3.2 Current trends in European bioethics	67
2.3.3 'True' knowledge and social awareness as crucial dimensions of medical ethics	67
2.3.4 "Primum non nocere" and "think harm always"	69

2.3.5 “Corruptio optimi pessima” and the power(s) of goodness 76

2.4 The nature of medical technology 79
2.4.1 Conceptualising medical technology 79
2.4.2 Heidegger on technology: Questioning builds a way 81
2.4.3 Technology and values 83
2.4.4 Ways in which technology is value-laden 84
2.4.5 Who is in control – the doctor or the tool? 86
2.4.6 Introduction of new medical technology – a history lesson by Ann Oakley 89

3 THREE CLINICAL ARENAS STUDIED IN THIS THESIS 90
3.1 Antenatal screening and diagnosis by ultrasound 90
3.2 Prevention of cardiovascular disease in clinical practice 91
3.3 The medical consultation in primary care 94

4 AN ANALYTICAL FRAMEWORK TO GUIDE FURTHER DISCUSSION 97
4.1 On the moral responsibility of medical professionals 97
4.1.1 What does it mean to be a professional? 97
4.1.2 The reflective practitioner 101
4.1.3 “Once the rockets are up – who cares where they come down”: on the moral responsibility of scientists 102
4.1.4 Heidegger on causality and responsibility 103
4.1.5 Einstein: a man of conscience 105
4.1.6 Hans Jonas on medicine, technology and responsibility 106

4.2 The concept of sustainable development 107
4.2.1 Historical background and definition 107
4.2.2 General prerequisites for sustainable development 109

4.3 Man as ‘standing-reserve’? 111

5 LIST OF PAPERS 116

6 AIMS OF THE STUDY 116

7 MATERIAL AND METHODS **118**
7.1 Outline of the premises of my research process 119
7.1.1 Exploration of the scientific literature 119
7.1.2 Arenas for critical reflection and 'respectful dialogue' 120
7.1.3 "Conversations with the situation" 122

7.2 Methodological information pertaining to the individual studies not outlined in the published papers 124
7.2.1 Paper I 124
7.2.2 Paper II 128
7.2.3 Paper III 132
7.2.4 Papers IV and V 132

8 RESULTS **136**
8.1 Synopsis of Papers I-IV 136
8.2 Overview of the results 142

9 DISCUSSION AND IMPLICATIONS **145**
9.1 Medical responsibility – promoting just and fair healthcare 145
9.2 Criteria for sustainable and responsible preventive medicine 148
9.3 Balanced theoretical approach 150
9.3.1. The characteristics of humane medicine 151
9.3.2 From 'evidence-based' to 'adequate' recommendations? 153
9.3.3 From Cartesian dualism to the Lived body 155
9.4 Environmental precaution: minimising adverse effects of medical activity 157
9.5 Equity: balancing the doctor's and the patient's agenda 161
9.5.1 The 'carrying capacity' of the consultation 162
9.5.2 Patients and doctors as moral strangers? 163
9.6 Democratic goal-setting, participation and policy integration 166
9.6.1 Before choosing health, choose your philosophy 167
9.6.2 Defining visions, goals and means for preventive initiatives 168
9.6.3 Evidence-based guidelines versus reality-based 'mindlines' 171
9.6.4 Some notes on the process of guideline development 174

9.7 Planning for the future: closing remarks 179

EPILOGUE **184**
On existential ground 184

10 LITERATURE **188**

11 PAPERS I-V
Paper I 213
Paper II 227
Paper III 235
Paper IV 239
Paper V 247

12 APPENDICES **253**
12.1 English translation of relevant HUNT 2 survey questions. 253
12.2 From antiquity to the foundations of EBM: some historical notes and personal reflections on the premises for contemporary medical consultations 254
12.3 Ultrasound screening for Down syndrome: a brief historical overview 269
12.4 Cardiovascular disease prevention in clinical practice: historical time-line 274

ABSTRACT

Background and setting Health care has become one of the most expansive activities in contemporary societies, and technology is one of its most influential factors. The modern medical-technological enterprise is however facing unprecedented practical, ethical and epistemic challenges. This thesis arises from a well-founded concern that medicine in general, and individually targeted preventive medicine in particular, may be about to become technified and dehumanised to an extent where its integrity and therapeutic as well as preventive potential may deteriorate.

Aims The paramount objective of this project is to contribute to critical reflection and theory building in medicine by performing a systematic documentation, analysis and conceptualisation of possible unacknowledged ethical dilemmas arising from implementation of advancing, preventive, individually targeted medical technology in clinical practice. A secondary aim is to present "sustainable and responsible development" as a potential framework for addressing ethical and practical challenges of this kind.

Theory, methods, and material Medicine is a moral enterprise. This renders all medical research and practice basically value-laden activities. The important implications of this fact are currently not fully recognised among medical researchers and clinicians. This thesis represents an integration of five different studies into a theoretical reflection concerning the inevitable and partly neglected value-ladenness of medicine. According to this position and following the tradition of the humanities, the researcher's frame of references is presented first, indicating the perspectives from where she wants her work to be regarded. The argument departs from the definitions and goals of medicine and comprises six fields of knowledge relevant for a theoretical exploration of the these goals: the concept of 'health'; the nature of medical knowledge and 'evidence'; the notion of 'medical ethics'; the characteristics of medical technology; and finally, the topics 'professional responsibility' and 'sustainable development'. The studies together address three distinct areas of clinical practice: ultrasound screening for chromosomal aberrations in the fetus, cardiovascular disease prevention in clinical practice, and the consultation in primary health care.

Results All five studies in this thesis demonstrate that implementation of new, preventive medical technology at the interface between individually and population-oriented care can bring forth important and complex ethical dilemmas and even harmful consequences. The results of the papers can be condensed under the following headings: 1. issues related to the theoretical foundation of contemporary, individually based, preventive medicine; 2. topics inherent to applying evidence-based medicine to individual patients; 3. issues related to practical sustainability and the carrying capacity of the healthcare system; and 4. issues of professional responsibility for both knowledge production and implementation of research findings in clinical practice, – the latter heading representing a meta-perspective.

Discussion The results of the five papers are introduced and discussed with reference to teachings and concepts originating from philosophers and medical scholars, such as Martin Heidegger, Hans Jonas, Michel Foucault, Charles Taylor, John Rawls, Arthur Frank, Drew Leder, Ian McWhinney and Eric Cassell. Furthermore, the findings are discussed within a framework that outlines a series of prerequisites for a sustainable and responsible preventive medicine:

- *A balanced theoretical approach to medical practice* implies that a comprehensive body of medical knowledge about the human condition must build upon both the natural sciences and the humanities.
- *Environmental precaution* means, in this context, that potential detrimental side-effects of medical activities must be systematically anticipated, supervised and kept at a minimum.
- *Equity* addresses, in this context, the importance of keeping a sound balance between doctor-initiated, technological preventive activities aiming at 'population care' and medical activities that are directed by the expressed problems, concerns or wishes of people seeking care or advice.
- *Democratic goal-setting, participation and policy integration* mean that all relevant stakeholders should be involved in defining, coordinating and evaluating the overall vision, philosophy and strategies of preventive medicine. Preventive recommendations in particular areas need to be harmonised and prioritised in accordance with an overall vision, and the expected impact of new

recommendations on clinical practice should be estimated before guidelines are issued.

- *Planning for the future* means, in the current context, that we should remember that our priorities and actions ought to appear justifiable and reasonable, not only from the point of view of evidence-based medicine as it appears here and now, but also as regarded from a more distant or even global perspective, or by the generations that will follow us who are making medical reality today. To achieve this, we need to continuously consider to what extent the scientific questions we ask and the decisions we make as professionals are concordant with what rings true and is important to us as fellow human beings.

Key messages and implications The knowledge foundation of modern preventive medicine, targeting individual persons/patients in the context of the traditional clinical encounter, is currently too limited and thus an inadequate basis for clinical action. Ethical deliberation regarding the medical activities explored in this thesis has also been deficient. Despite the medical profession's explicit intention of doing good, these two fundamental shortcomings imply a potential for inflicting medical harm. This inherent danger imposes the imperative of a paramount responsibility on medical researchers, administrators and practitioners. The practical and ethical impact of technological innovations in preventive medicine should be subjected to systematic and comprehensive analysis. Each particular new technology ought to be evaluated as for its own characteristics and consequences. It should also be measured against the overall goals, means and priorities of preventive medicine. These ought to be clearly defined and made accessible to critical scrutiny and open debate.

PREFACE AND ACKNOWLEDGEMENTS

When I decided to study medicine in 1982, I envisioned the discipline as majestic and humble. Today, I still think medicine is an impressive and powerful enterprise. But rather than humble, I have come to see it as self-assertive and expansive, and to a greater extent than I believe is good for human health. As a result, I feel professional unease.

This PhD thesis builds on a synthesis of experience-based, reflection-based and empirically-based knowledge development. This methodological approach has posed a challenge, as will be described in the methods section. I have often wondered why I had to embark on such a complicated project, instead of doing mainstream research which makes for a smooth career. The best explanation I can come up with is that I was brought up by a father who encouraged me to think rationally and independently, even in the face of expert opinion, whilst my mother, on the other hand, taught me the importance of relation, dialogue and intuition (see Epilogue).

This thesis ends with a set of voluminous appendices presenting historical facts, events and trends in the three clinical fields that are explored in the five studies. It would not have been possible to conceptualise ethical dilemmas in contemporary medicine in the absence of considerable knowledge about the clinical activities in question. As I explored these areas to considerable depth, I made notes – mainly for my own sake. My supervisors, however, found the resulting documents interesting and advised me to make them accessible to interested readers. The appendices should be regarded as 'working documents' and not as strictly scientific presentations.

The origins of this project

The person who first woke my interest in academic medicine at the interface between mathematics and meaning was Steinar Westin, professor of social medicine at Norwegian University of Science and Technology (NTNU). He taught us students – in a manner that I still find memorable – how cultural reality can be mirrored in medical statistics: The details of the mortality figures from the *Titanic's* shipwreck make no sense un-

less you consider the impact of social class and gender on people's destiny. After that lesson, Steinar became my mentor.

This entire project was originally planned to be about prenatal diagnosis; an arena where facts and meaning are more closely interwoven than perhaps anywhere else in medicine. The idea of investigating the topic of soft markers for fetal anomaly was my own. I nevertheless want to thank Rigmor Austgulen, Berge Solberg and my colleagues at the Department of Public Health and General Practice at NTNU for encouraging me to investigate the esoteric knowledge field of fetal soft markers.

As can be seen from the list of papers, the present thesis is not only about prenatal diagnosis. This is because some of the key actors in the field of prenatal medicine – whom I would depend on cooperation with – did not accept the way I conceptualised ethical challenges. To make a long story short, I decided it would not be wise to pursue my ideas related to prenatal diagnosis further. So I called the project off. In connection with this difficult decision, I met with Gunnar Bovim and Tore Lindmo as representatives for my employer NTNU. I was received in a very respectful and trusting manner. This inspired me to look for a revised project.

Before closing the project on prenatal diagnosis, I completed the comprehensive theoretical analysis I had already embarked on (which is Paper I in this thesis). And whilst this work was done, Kjell Åsmund Salvesen, who was at the time working at the National Centre for Fetal Medicine in Trondheim, helped me sort out the numerous technical questions I had regarding the issue of soft markers for fetal anomaly.

Supervisors and collaborators on the revised project

When I left the prenatal diagnosis project, I started in my current position as a staff physician at the Landspítali University Hospital in Reykjavík. Shortly thereafter, Irene Hetlevik and Niels Bentzen – whom I did not really know then – invited me to present a keynote lecture at the 12th Nordic Congress in General Practice in Trondheim in 2002. The resulting collaboration was inspiring and resulted in Papers II and III in this thesis. Then, in 2003, Irene contacted me and said she had come to realise that my recent writings could in fact be seen as constituting

a whole, if regarded from a theoretical rather than a clinical viewpoint. She suggested I conduct two studies on cardiovascular disease prevention, and the list of papers would be complete. She offered to be my supervisor. I immediately liked her idea, and suggested that Anna Luise Kirkengen co-supervise the project. Thereby, the research triangle, Academia Mobile, was established.

Academia Mobile (Irene, Anna Luise and I) have met to collaborate intensively on two occasions. In 2004, we spent a week in Tolfa, Italy; and in the winter of 2005, we spent a short week in Budapest. These academic workshops have combined penetrating discussions, long walks, cultural activities and culinary highlights. These have been the most creative experiences of my professional life. During the long periods in between when I have worked on my own, Irene's clear vision, down-to-earth approach and admirable determination have helped me stay on-target. In daily life, I have often consulted Anna Luise as an academic mastermind, both via e-mail and personal meetings. The combination of Irene's steady, gentle and determined pull and Anna Luise's formidable knowledge and generosity resulted in the best supervision any PhD candidate could wish for. But I also want to acknowledge the assistance from my co-workers on papers IV and V: Professor Jostein Holmen and researcher Solfrid Romundstad at the HUNT Research Centre in Verdal, as well as my husband Jóhann Ágúst Sigurðsson, professor in Family Medicine at the University of Iceland. Without Jóhann's magic blend of supportive academic interest and practical assistance, this thesis would not have been written.

Other supportive individuals and environments

Due to my relative isolation during the writing process and the somewhat controversial nature of my academic activities, it has been essential for me to feel part of a greater whole. As will be outlined in the methods chapter of this thesis, I have, between 2001 and 2005, been greatly inspired by the *Rosendal seminars*, arranged by *Filosofisk poliklinikk* in Bergen. In a similar manner, I have benefited from participating in two congresses of philosophy in medicine (Krakow 2000 and Barcelona 2005). Discussions with fellow speakers and participants in these settings have meant a lot to me. For the last couple of years, I have also been a member of the *Bioethics Research Group* at NTNU, and

this resourceful, interdisciplinary academic network has been an inspiring link to NTNU. I also want to acknowledge the support from fellow members of the *Nordic Risk Group* (NRG, established in 2003), which is a group of academically active Nordic general practitioners sharing the vision "to promote general practice which is salutogenic, empowering and sustainable."

Many individuals come to mind whom I would in particular like to thank. But I would hardly know where to stop if I started listing names. Many colleagues and co-workers in clinical practice and academic settings have inspired and encouraged me, in big and small matters. I am also sincerely grateful to several researchers in other disciplines, in particular philosophers, who have opened my eyes to other academic universes.

Financial support
The original project received a research grant from the *Norwegian University of Science and Technology* (NTNU) in 1999. From 2001 through today, I have been employed as a staff physician at the Landspítali University Hospital in Reykjavik, and Papers II-V have all been written in my spare time. As I approached the closing phase of the project in 2005, I received a grant from the *Norwegian College of General Practitioners* (NSAM – allmennpraktikerstipend) as well as a grant from *Nidarosfondet til fremme av allmennmedisinen* i Midt-Norge. This made it possible for me to take some time off from my hospital work to complete this thesis. This project has also received financial support from *The Icelandic Family Physicians Research Fund* in Iceland and *The Bioethics Research Group* at NTNU. I thank my current employers at Landspítali University Hospital for giving me the flexibility needed to complete this work and for giving me access to the hospital's excellent library services throughout the whole project.

1. INTRODUCTION

Health care has become one of the most expansive activities in contemporary societies, and technology is one of its most influential factors. The modern medical-technological enterprise is however facing unprecedented practical, epistemic,[1] and ethical challenges. Many scholars and writers have, for different reasons and from different perspectives, called for systematic, critical reflection on the theoretical foundation, goals, means and limits of medicine (see, for instance, Skrabanek 1994; the Goals of medicine project, edited by Callahan in 1996; le Fanu 1999; Porter 1997; Murphy 1997; Kirkengen 2001; Abramson 2004; Tallis 2004).

1.1 Outline of this thesis

This thesis arises from a solidly founded concern that medicine in general, and individually targeted preventive medicine in particular, may be about to become technified and dehumanised to the extent that its integrity and therapeutic as well as preventive potential may deteriorate. Despite what appears on the surface to be the best of medical intentions – to prevent people from falling ill – the medical profession may be running the risk of undermining its own credibility and legitimacy in this important field. In this thesis, I will present a combination of theoretical reflections and empirically based writings concerning this issue. The paramount aim is to define, analyse and conceptualise unacknowledged ethical dilemmas which I perceive in relation to the clinical implementation of advancing preventive, individually targeted medical technology. A secondary aim of this study is to suggest an analytical framework for further discussion of this topic.

It is sometimes assumed that if one is not an unequivocal defender of reason, science and technology, then one is against them.[2] Opposition is far

[1] Epistemology, from Greek *epistEmE* knowledge, from *epistanai* to understand, know, from *epi-* + *histanai* to cause to stand (Merriam-Webster's dictionary 2005). The theory of knowledge; the branch of philosophy concerning the definition of *knowledge*, and the establishment of criteria for evaluating claims that something is known. See Ashcroft's paper *Current epistemological problems in evidence based medicine* (2004).

[2] In his *Letter on Humanism*, German philosopher Martin Heidegger regretfully notes how culture critics like himself tend to experience that "People ... immediately assume that what speaks against something is automatically its negation and that this is 'negative' in the sense of destructive (...) But does the 'against' which a thinking advances against ordinary position necessarily point toward pure negation and the negative? (...) Concealed in such a procedure is the refusal to subject to reflection this presupposed 'positive' in which one believes..." (The full quote appears in a paper titled *Escaping technological nihilism*, see Milchman and Rosenberg 2003:55).

from my position. I fully acknowledge that modern medicine possesses an unprecedented capability for saving people from untimely death and for improving the lives of people suffering from chronic disease and disability. The therapeutic revolution in modern medicine represents an impressive human endeavour. In a sense, I personally owe my life to the advances of medical technology, and I am gratefully aware of this.[3] The potent and truly benevolent powers of modern medicine are, however, not the topic of this study. This is a thesis about *problematic issues in modern preventive medicine*.

Many scholars, researchers and clinicians have written that they see dehumanising, medicalising, coercive, and even corrupting forces in modern preventive medicine (Illich 1976; Skrabanek 1994; Moynihan and Smith 2002; Moynihan, Heath and Henry 2002; Abramson 2004; Angell 2004). I do not aim to present an extensive overview of this critique here. I will simply set the scene by quoting a short series of authoritative voices lending breadth, weight and legitimacy to my professional concerns.

The rest of this introductory part will be devoted to theoretical perspectives, concepts and discourses to help readers see *that the five papers in this thesis rest on common theoretical grounds*. The papers refer to three different clinical 'scenarios'; ultrasound screening for fetal anomaly, cardiovascular disease prevention, and the clinical encounter in primary health care. They also represent five different genres of scientific writing. However, if regarded from a theoretical viewpoint, they deal with common epistemological and ethical topics, as can be seen from the schematic overview of results in chapter 8.2. I follow the tradition of the humanistic sciences as I begin by introducing my own theoretical position, and from this position, the theoretical viewpoints from which I would like my work to be regarded. I then, present the research as such. The organisation of this thesis is illustrated in Figure 1.

[3] See the Epilogue to this thesis.

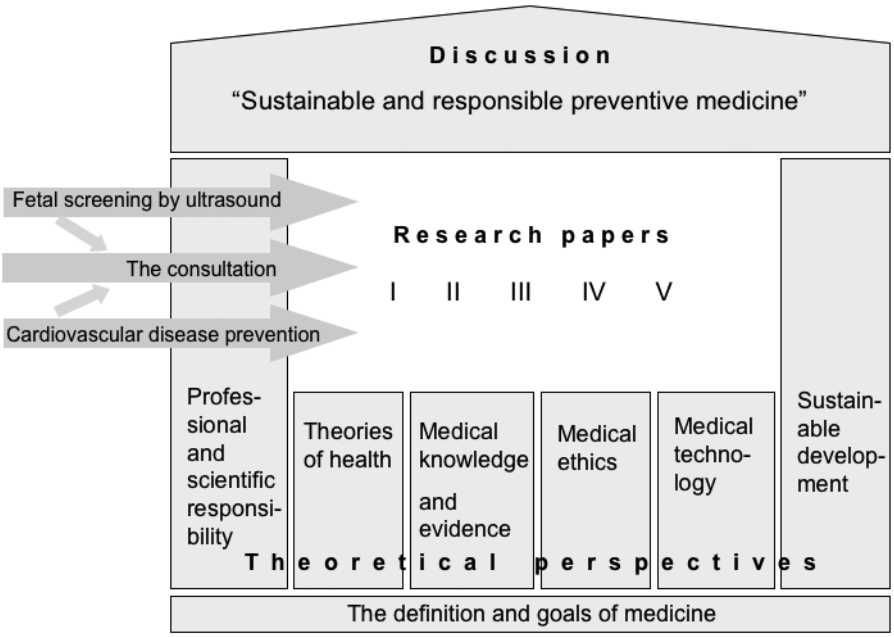

Figure 1. *The organisation of this thesis.*

The format of this PhD thesis is unusual in the biomedical context. The reason is that it contains critical reflections in relation to modern preventive technologies. Such reflections can hardly be put forward meaningfully in a format which has been developed to accommodate, hand-in-glove, the scientific premises that are laid out by the very same technology. My decision to go theoretically and methodologically "off the beaten track" can, as I see it, find support in the thoughts of German philosopher Martin Heidegger (1889-1976), one of the 20th century's most influential thinkers regarding modern technology (see further description in chapter 2.4.2). In his 1953 essay *The Question Concerning Technology* (Heidegger 1977:35), Heidegger stated:

> Because the essence of technology is nothing technological, essential reflection upon technology and decisive confrontation with it must happen in a realm that is, on the one hand, akin to the essence of technology, and on the other, fundamentally different from it.

In the same essay, Heidegger stated that "questioning builds a way" for those who, like him, feel an urge to reflect upon what modern technology means to human beings, for better or for worse. This thesis can best

be characterised as an example of 'Heideggerian questioning' of contemporary, individually based, preventive medical technology.

As said above, I intend to emphasise the interrelatedness of the five papers in this thesis. Therefore, I will focus on theoretical perspectives rather than chronological developments in this introduction. I have however paid considerable attention to chronology and historical developments when preparing this thesis. Interested readers may find notes from my "field works regarding chronology" in the appendix section.

The theoretical discourses and concepts covered in the following introductory chapters, include:

- the concept of 'health',
- the nature of medical knowledge and 'evidence',
- the notion of 'medical ethics', and
- the characteristics of medical technology.

Towards the end of this chapter on theory, three scenarios, representing three distinct fields of clinical practice of the above-mentioned topics, are presented. These clinical scenarios are analysed in Papers I-V in this thesis. Each of these fields has its own historical background, chronological development and body of scientific literature, and this is addressed in appendices 2-4.

Since one aim is to suggest an analytical framework for further discussion and tackling of the dilemmas that are described in the five papers, the final entry in the theoretical section will present the concepts of

- professional responsibility, and
- sustainable development.

An analytical framework based on responsibility and sustainability might, in my opinion, help medical professionals and healthcare administrators acknowledge, understand and tackle some of the challenges that modern preventive medicine is currently facing. These concepts will therefore structure the discussion part of this thesis.

The term *sustainable development* (see chapter 4.2) should not be unfamiliar to Norwegians. It was brought to world-wide attention in 1987 in the World Commission report *Our Common Future* (1987), better

known as "the Brundtland Report" after former Norwegian Prime Minister Gro Harlem Brundtland, medical doctor and chairman of the World Commission on Environment and Development. In its time, *Our common future* focused political attention on the concept of sustainable development as an analytical tool to guide discussions about growth and development. Since then, sustainable development has been explored from various perspectives by different academic disciplines. However, the medical community has hardly addressed the topic. The only systematic attempt to do so that I have come across stems from medical philosopher Daniel Callahan and co-workers, who have outlined some general characteristics of a sustainable medicine, with particular reference to the US context (see Callahan 1996 and, in particular, Callahan 1999).

1.2 Voices of concern

Several scholars have pointed out that *contemporary medicine appears to be losing sight of its goals and limits*. In 1997, Roy Porter, professor in the social history of medicine, published a widely appraised book titled *The greatest benefit to Mankind. A medical history of humanity*. The last phrase of Porter's book reads as follows (Porter 1997:718):

> The close of my history suggests that medicine's finest hour is the dawn of its dilemmas. For centuries medicine was impotent and thus unproblematic. From the Greeks to the first World War, its tasks were simple: to grapple with lethal diseases and gross disabilities, to ensure live births and manage pain. It performed these with meagre success. Today with 'mission accomplished', its triumphs are dissolving in disorientation. Medicine has led to inflated expectations, which the public eagerly swallowed. Yet as those expectations become unlimited, they are unfulfillable: medicine will have to redefine its limits even as it extends it capacities.

On January 14th 2006, the *British Medical Journal* featured a series of articles regarding implementation of new interventions in health care. It is acknowledged that "technological innovations drive modern health care at an accelerating pace," and that introduction of medical technology can suffer from both too much too soon and too little too late. Careful monitoring of the transition zone between technological development and clinical implementation is therefore important. As Gabbay and Walley (2006) state:

> The social processes of diffusion can turn "technology creep" into widespread practice before health technology assessors can even define, let alone evaluate, new healthcare interventions; but those same processes can result in important de-

velopments being ignored and underused…. Conflicting interests with deeply held values inevitably affect every stage of healthcare innovation.

In 2005, the newly appointed editor of the British Medical Journal Fiona Godlee expressed explicit concerns over current developments in preventive medicine in the journal's column *Editor's choice*, under the title *Prevention makes us miserable* (BMJ, April 23rd 2005):

> The old adage – prevention is better than cure – is one we have heard so often that it's hard to shift from our minds. It is intuitively powerful. It just seems to make sense. But shift it we must, for it fuels (...) "the excessive self confidence of preventive medicine," which is making us ill and miserable.

Several scholars have noticed that, at some point, *more medicine may become worse medicine*. In 1999, US researchers Elliott Fisher and H. Gilbert Welch published a seminal paper in the *Journal of the American Medical Association*, where they claimed that (Fisher and Welch 1999):

> While the benefits of more medical care are widely recognised, the possibility that harm may result from growth has received little attention. Because harm from more medical care is unexpected, findings of harm are discounted or ignored. We suggest that such findings may indicate a more general problem and deserve serious consideration.

Various authors have pointed out that *there is a need for integration of, and a clearer philosophy in relation to, preventive medical activities*. Two quite different papers can illuminate this topic. In 2003, an American research group published a modelling study documenting the aggregated impact of providing all recommended services, as outlined by the *US Preventive Services Task Force*. The finding was that implementation of these recommendations would require no less than 7.4 hours of each primary care physician's working day (Yarnall et al. 2003). In 2002, two professors of public health published a paper in *The Lancet* where they called for the deliberate use of philosophy in relation to planning strategies to improve population health (Roberts and Reich 2002):

> Public health today grapples with issues rife with ethical dilemmas and political conflict (...) Yet public health professionals have minimal training in ethical analysis. If health professionals are to develop coherent positions on these issues, and contribute to democratic deliberation about public policies, then they need enhanced skills in applied philosophy. Understanding alternative ethical arguments has become as important as knowing the advantages and disadvantages of different epidemiological techniques.

In modern medicine, the notion of *risk* is central. The risk discourse stands in a somewhat paradoxical relationship to the honoured notions of freedom and autonomy. At the Norwegian conference *Cultural perspectives on risk, preventive medicine and health promotion* in 2003 (proceedings edited by Grimen and Elvbakken 2003), Swedish sociologist Eva Palmblad spoke about a phenomenon which she called "the art of social engineering". Social engineering, she claimed, used to be implemented by paternalist, expert dictate. In contemporary society, however, it has come to operate in the name of freedom, autonomy and self-techniques. In accordance with French intellectual and historian Michel Foucault's (1926-1984) theory on *medical policing* (Foucault 1975), Palmblad perceives that people may thereby currently be subjected to new and subtle forms of social control (Palmblad 2003):

> It is said that today's citizen has attained a historically unique right to make his or her own choices with a bearing on health and well-being. It may concern everything from eating and exercise habits to sexuality and childbirth. For example, today we can choose not only *if* and *when* we want children; with the aid of fetal diagnosis we are also in position to consider whether we want *that particular* child.
>
> But something happens: As soon as we have been granted the *right* to choose, it tends to change into a *duty* to choose – and furthermore to make rational choices, seen in relation to the general good of the society and succeeding generations. Freedom seems, in this way, often to be defined instrumentally, in such a way that it becomes a pre-condition for the success of health policy.

This calls to mind the writings of Czech toxicologist, and later Professor of Community Health in Dublin, Petr Skrabanek. In 1990, he asked *Why is preventive medicine exempted from ethical constraints?* (Skrabanek 1990). He believed that healthy people taking part in preventive mass interventions are in fact "subjects of large-scale population experiments of uncertain outcome and potential harm". So why are these interventions not evaluated by ethical committees? Skrabanek points to historical and political reasons for what he calls "the ethical vacuum of preventive medicine". Early preventive medicine in the 19th century dealt with contagious diseases and was synonymous with medical policing. Skrabanek's opinion was that modern preventive programmes are of a completely different nature, thus calling for original ethical analysis.

Only a few days before his death from aggressive prostate cancer at the age of 53, Skrabanek finished the manuscript of his book *The death of humane medicine and the rise of coercive healthism* (Skrabanek 1994).

He wrote:

> The pursuit of health is a symptom of unhealth. When this pursuit is no longer a personal yearning but part of a state ideology, healthism for short, it becomes a symptom of political sickness (...) All totalitarian ideologies use the rhetoric of freedom and happiness, with false promises of a happy future for all.

Two sociologists recently published a comprehensive analysis of the development of the doctor-patient-relationship. They claim that *superficiality* is a characteristic of contemporary medical practice (Potter and McKinlay 2005):

> Compared to the 20th century where doctor-patient relationships could be characterised by depth and history, the 21st century relationship between a doctor and a patient can increasingly be characterised by superficiality and focused on the here and now.

In 2004 Samuel LeBaron, Director of the Center for Education in Family and Community Medicine at Stanford University School of Medicine, published a paper titled *Can the future of medicine be saved from the success of science?* (LeBaron 2004). He notes:

> …an emphasis on the achievements of biomedical science has contributed to loss of human understanding and increased cynicism and dissatisfaction in medicine. A balanced approach to health care requires attention to both the biological and humanistic aspects of our patients' lives.

1.3 Definition and goals of medicine

According to the Merriam-Webster Dictionary (2005), medicine is defined as

> the science and art dealing with the maintenance of health and the prevention, alleviation, or cure of disease.

This definition is congruent with my own view. I am also willing to regard "prevention, alleviation, or cure of disease" as summing up the paramount *goals* of medicine as a whole.

In the following, the term 'medicine' will be applied in two different but interconnected ways:

1. to designate *a moral, altruistic institution* – existing for the purpose of helping people. The medical profession and its associated

organisations and practices are thereby conceptualised as an abstract, yet morally responsible, 'agent'.
2. to designate *a circumscribed body of theoretical assumptions, factual knowledge and research methods*, together encompassing the so-called "biomedical paradigm".

1.3.1 Curative versus predictive and preventive medicine

The idea that prevention is better than cure appears intuitively attractive, and hardly in need of philosophical or scientific defence. And in fact, the most renowned ideologist ever in the area of preventive medicine, epidemiologist Geoffrey Rose, anchored his vision in a very commonsense way as he said (Rose 1992):

> It is better to be healthy than ill or dead. That is the beginning and the end of the only real argument for preventive medicine. It is sufficient.

It is important, however, to acknowledge the fundamental difference between *curative* and *predictive-preventive* medicine. Furthermore, as underlined by Petr Skrabanek, *traditional preventive medicine* is something distinctly different from more recent preventive activities, which he designated as "anticipatory care", "proactive medicine" and "health maintenance." To traditional *preventive medicine* he assigned vaccinations, pasteurisation, and stopping the spread of contagious disease.[4] Prevention of this kind is cause-specific and empirically and pragmatically based. Modern *proactive medicine*, on the other hand, is aimed at multifactorial conditions and is based on theoretical calculations of *risk (prediction)*. Intervention in relation to disease risk evokes many metaphysical questions that are not raised by curative medicine and traditional preventive medicine.

It may well be that Skrabanek's nuanced vocabulary would help us advance the discussion of ethical dilemmas relating to preventive medicine. It has however not entered mainstream medical language, so I decided to use only the terms *preventive* (synonym: preventative) or *predictive* medicine in this thesis.[5]

[4] This thesis does not address preventive interventions of this type.

[5] I will make no sharp distinction between the terms predictive and preventive. Predictive medicine may be a better term to designate personalised interventions related, for instance, to genetic testing, fetal ultrasound screening with computerised risk estimates, or application of a cardiovascular disease risk calculator. The term predictive also circumvents the verbal dilemma arising in relation to prenatal diagnosis, where the most common intervention is termination of the pregnancy.

This study addresses preventive medical activities involving standardised measurement, evaluation and counselling related to selected parameters known to vary between individuals. Examples of such variables are the biological parameters of blood pressure, cholesterol, bone mineral density, and fetal nuchal translucency.

As previously pointed out, the moral foundation for preventive/predictive initiatives aiming at improving health among people who are currently free of symptoms is different from the moral foundation of curative medicine that is offered to patients seeking medical help for problems they are currently experiencing (Skrabanek 1990; Ewart 2000; Mallia and Ten Have 2003). In a paper called *The arrogance of preventive medicine*, David Sackett – founding father of evidence-based medicine (EBM) – has emphasised that preventive and curative medical activities are "absolutely and fundamentally different in their obligations and implied promises to the individuals whose lives they modify" (Sackett 2002).

1.3.2 Discourse on medical risk

As outlined by Armstrong (1995), medicine's primary focus, in the preceding 300 years, has gone through various stages. Eighteenth century bedside medical practice relied on *symptoms* and aimed at dealing with the patient's subjective illness. Nineteenth century hospital medicine and early 20th century medicine in general was mainly concerned with *signs* and focused on the objective disease hidden in the patient's body.[6] In the late 20th century, medicine became gradually more concerned with threats of future disease, and thereby started to conceptualise the notion of medical *risk*.

Since the 1970s, a phenomenon which Norwegian scholar John-Arne Skolbekken has termed a "risk epidemic" has developed in biomedical research and publishing (Skolbekken 1995). Understanding the occurrence of disease in terms of *risk* is a modern phenomenon (Ogden 1995; Armstrong 1995; Kavanagh and Broom 1998). It can be seen as a particular manifestation of the general risk discourse characterising modern, industrialised societies, and perhaps even more, the post-modern world we can currently be seen as living in (Blaxter 2004).

[6] See Appendix 2 for further description of this historical development.

In 1992, German Professor of Sociology Ulrich Beck coined the descriptive term *risk society* (Beck 1992). Beck suggests that we live in a society which is increasingly interdependent and increasingly vulnerable to international catastrophe and to the risk management of organisations over which we have no control. Health risks – especially ecological, genetic, nuclear, but also economic risks associated with global economies – are in the hands of experts whose manner of assessment we may not even understand, and whom we may not trust. The erosion of trust is fostered by the growing recognition that these risks are often ultimately unknowable. Mildred Blaxter, UK professor of social medicine, emphasises that there is, of course, nothing new about the fact that life presents continual risks to the life and health of the individual. What is new, however, is that the imposition of technological risks is recognized, publicized, feared and resisted by the population (Blaxter 2004).

In the modern, as opposed to what is now called the post-modern, world, risk was mainly a basic concept of epidemiology in the form of statistical risk factors for morbidity and mortality (Blaxter 2004). This approach saw risk as a technical matter to be tackled with more science and better public information. From this point of view, a basic premise was that all risks are measurable and possible to control. And towards the end of the 20th century, a whole industry developed, concerned with risk, risk assessment and risk intervention. Risk assessment gradually became a key element of public health, and risk discourse became "the language of health education" (Blaxter 2004). The interest in risk has also had a profound impact on clinical medicine (for a critical perspective of this development in the Norwegian medical context, see, for instance, Holmen 1994). Appreciation of risk is, to an increasing extent, the means by which each individual is encouraged to evaluate and regulate his or her life and body, and this encouragement is associated with ideas of *choice* and individual *responsibility*.

In general, lay people's ways of understanding risks tend to differ from those of experts. The psychology of risk perception and the relationship between lay and expert perceptions of risk has thereby become a prolific field of research (Blaxter 2004). Ample research shows that the risk concept is hard to handle, also in the particular context of medicine. It is complex, relatively poorly understood by health professionals, and correspondingly difficult to communicate to the individual patient (person)

in a meaningful way (see, for instance, Hetlevik 1999; Lewis et al. 2003; Michie et al. 2005; Herxheimer 2005).[7] In relation to preventive medicine, the notion of health currently represents an increasing epistemological challenge. Blaxter observes that the presence of statistical risk factors, such as smoking, overweight and a sedentary life style, is about to become equivalent to a diseased state – calling for individual therapeutical intervention. Correspondingly, the traditional terms 'normal', 'at risk', 'abnormal' and 'pathological', so essential to modern medical discourse (Canguilhem 1966; Hofmann 1995; Horton 1995; Adelsvärd and Sachs 1996; Trnka 2003), are becoming blurred (Armstrong 1995; Blaxter 2004). Papers I, IV and V of this thesis address this topic. In particular, Papers IV and V show how the risk definitions in the current guidelines on cardiovascular disease prevention (de Backer et al. 2003) render it normal (i.e., the most common or 'average' state) to have an unfavourable risk profile. In the context of one of the world's most long-living and healthy-living populations (Norway), this finding poses fundamental questions: What are the ultimate goals of individual versus collective preventive medicine? To what extent is such an interpretation of human health basically sound, pragmatically sustainable and morally responsible?

In everyday primary medical care in the Western world, there is little doubt that resources have recently, and to an increasing extent, moved from *currently sick people* to people who are *currently free of symptoms*, with the aim of preventing future disease. To illustrate this, I will quote a UK general practitioner who recently wrote to the *British Medical Journal* (BMJ) (Spence 2005):

> This pursuit of risk avoidance has become the mantra of health care and is now a political manifesto pledge. Indeed the new GP contract is a distillation of risk management, neatly reinforced by rigorous cost-benefit analysis.

Individually oriented preventive medical initiatives that are founded on risk calculations are typically characterised by fragmentation (Getz 2001 i), biological monitoring and technological interventions. They may be of proven *efficacy* in the research setting, but there may still

[7] There are many references to the topics of risk perception and communication. Three examples are Skolbekken J-A. *Communicating the risk reduction achieved by cholesterol-reducing drugs* (BMJ 1998;316:1956-8), a BMJ theme issue *Communicating risks: illusion or truth* (27 Sept 2003), and Halvorsen P, Sønbø Kristiansen I. *Decisions on drug therapies by numbers needed to treat.* Arch Intern Med 2005;165:1140-6.

be limited – or even no – evidence of their *effectiveness* in 'free-living populations' (Hetlevik 1999; Lindeberg 2005). In terms of consequences for the individuals, the healthcare system, and society-at-large, there has been very little debate about the 'down-stream' effects of medicine's massive ambitions to modify risk factors among currently healthy, or at least asymptomatic, individuals (Grimen and Elvbakken 2003; Hetlevik 2004).

I will close this general introduction with a quote from Norwegian scholar Bjørn Hofmann. Along lines similar to my argument, Hofmann emphasises that in comparison to curative medicine, predictive-preventive medical testing "represents a fundamental epistemological and evaluative change in medicine". He thereby supports my claim that we need to scrutinize modern preventive medicine from an ethical viewpoint. In the same paper, which is titled *On the value-ladenness of technology in medicine*, Hofmann continues by saying (2001:338):

> Medicine's independence of the patient's illness gives health care unrestricted power to prescribe treatment. Misuse of such power is not hard to imagine, and how to manage this power is obviously an evaluative challenge.

2. THEORETICAL PERSPECTIVES

2.1. Conceptualising health

In Western countries, medicine is practiced in the context of a "health-care system." In the conclusion to his thesis *The technological invention of disease – on disease technology and values* (2002), Hofmann notes that this system might more appropriately be termed a "disease control, illness and sickness rights system" (Hofmann thesis 2002:57), since modern medicine does not rest on any comprehensive theory of the nature of human health.

Health, like faith, love, beauty and happiness, is a metaphysical concept eluding all attempts of objectification. It is something we learn to appreciate fully only when it is no longer there. Petr Skrabanek put this notion to its limits as, shortly before his death, he maintained that "healthy people do not think about health" (Skrabanek 1994). In her 2005 book *Health*, Mildred Blaxter notices that "Health may be defined differently by doctors and their patients, and over time and place..." She discusses how health can be conceptualised and 'operationalised' in various ways: as the absence of illness, the ability to function, balance or homeostasis; as a biomedical construct or a social construct (Blaxter 2004). It is also relevant to note that what constitutes a 'good' definition of health may depend on context. A comprehensive and visionary definition of health may, for instance, serve certain political and strategic purposes, whilst appearing utopian in relation to the health of any particular individual. The controversial definition issued by the World Health Organisation in 1948 can be regarded as an example of this:

> Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

I will not discuss this WHO definition further here.

Several philosophers have presented their personal definitions of health throughout the years. Among them is the Swede Lennart Nordenfeldt who in 2001 defined health in the following manner (quoted in Grimen and Elvbakken 2003:55):

> Health is the bodily or mental state of a person which is such that he or she has an ability to realize vital goals, given standard or otherwise acceptable circumstances.

What characterises Nordenfeldt's definition, alongside with other definitions of health presented by philosophically trained thinkers, is that it emphasises *subjective human aspirations, resources and possibilities*, whilst downplaying scientific biomedical evaluations of diseases, disabilities and diagnoses.

It is not an aim of this thesis to go deep into theories regarding health. All its five sub-studies, however, highlight that in contemporary clinical practice, significant dilemmas are bound to arise if one regards *absence of disease as a basic premise for health* and, perhaps, even goes so far as to extend the notion of health to include the *absence of significantly elevated risk for future disease*, as defined in biomedical terms. The main title of Paper II ("A matter of heart") was deliberately chosen to capture the tension between an immediate "disease-and-risk" versus a "health-and-resource"-oriented approach to one particular individual in clinical practice. "A matter of heart" refers, on the one hand, to "the body of correct biomedical evidence regarding secondary prevention of heart disease" and, on the other, to "the doctor's disheartening feeling of having inflicted existential injury on his patient by application of the best medical evidence."

In order to illuminate the epistemological roots of this tension, I will now review some definitions, models and conceptual frameworks shedding light on health. It is evident that these models differ fundamentally from mainstream biomedical reasoning.

2.1.1 The Goals of Medicine Project's definition of health

In 1996, the prestigious U.S Hastings Centre's ambitious, international and interdisciplinary "Goals of medicine project", directed by philosopher Daniel Callahan (Callahan 1996), published the following definition of health – an academic challenge to biomedicine:

> Health is the experience of well-being and integrity of mind and body.

The definition may appear intuitively attractive and innocent. However, closer consideration of it shows that it is alien to the theoretical knowledge base of medical doctors who have learnt to consider health in terms of the *absence of biological dysfunction*. The notion of "experiencing well-being" is an entirely subjective and individual position about which knowledge collected by methods striving for objectivity and generalis-

ability can say very little. The incompatibility increases by adding the term "integrity", which is an existential dimension and a philosophical concept belonging to the academic realm of the humanities. In the biomedical context, the concept of 'mind'[8] also makes limited sense, except that it points in the direction of *brain*. The difference between mind and brain is, however, that *mind* encompasses the experience of meaning, purpose, and ambivalence. It also gives room for existential categories, such as shame, despair, conflict, love, jealousy and hatred. *Brain* is defined in terms of *matter* only, i.e., neural centres, pathways and transmitters.

2.1.2 Antonovsky's model of salutogenesis

The second conceptualisation of health which I will present was developed by American-Israeli sociologist Aron Antonovsky in the 1970s and 1980s (Antonovsky 1987).[9] Antonovsky was interested in what keeps people healthy (*salutogenesis*), as opposed to the origins of disease (*pathogenesis*). Antonovsky was not interested in particular illnesses; he focused on factors that could describe a general ability to manage tension and stress, which he believed to be omnipresent in human existence. Originally, Antonovsky conceptualised this in terms of *general resistance resources* (GRRs). Subsequently, he developed his theory further and introduced the concept *Sense of coherence*. Antonovsky formulated sense of coherence (SOC) as (Antonovsky 1987):

> …a global orientation that expresses the extent to which one has a pervasive, enduring though dynamic, feeling of confidence that one's internal and external environments are predictable and that there is a high probability that things will work out as well as can be reasonably expected.

The key feature of salutogenesis is thereby *a general orientation towards problem solving and identification of available resources*. Antonovsky conceptualised coherence as consisting of three dimensions:

- *Comprehensibility*, meaning that the world appears ordered and understandable, as opposed to chaotic, arbitrary or inexplicable.
- *Manageability*, referring to a feeling that problems have solutions, and that life's demands can be tackled.

[8] Definition of mind: "the element or complex of elements in an individual that feels, perceives, thinks, wills, and especially reasons" (Merriam-Webster's Dictionary, 2005).

[9] To get a brief overview of and introduction to Antononvsky's original works, one may start by reading Lindström B, Eriksson M. *Salutogensis*. J Epidemiol Community Health 2005;59:440-2.

– *Meaningfulness*, the experience that life is challenging, and that things are worth investing energy in.

Antonovsky perceived that a strong sense of coherence was likely to lead a person to engage in constructive behaviours which promote health per se. But he also believed that a sense of coherence would affect the body's endocrine and immunological systems, thereby mobilising fundamental bodily resources (Antonovsky 1987):

> My hypothesis then is that the strength of the sense of coherence has direct physiological consequences and, through such pathways, affects health status.

Antonovsky did not see SOC as basically an inherited personality trait; rather, he saw it as a dispositional orientation strongly dependent on social circumstances and the socialisation in the individual's childhood and youth.

Based on his theory of health, Antonovsky developed a questionnaire which he called the "Orientation to life", or *Sense of Coherence Scale* (SOC scale), (Antonovsky 1993). By statistical standards, the scale has been found both valid and reliable. It exists in several versions and has been translated to more than 30 languages. It has been applied in various health research projects, investigating the relation between SOC, on the one hand, and psychological health, stress and behavioural aspects, physical health, biological measures,[10] on the other. A low SOC has repeatedly emerged as strongly associated with poor mental health, particularly measured as anxiety or depression. No consistent relationship has however been documented between SOC and physical health (Bengel et al. 1999). A Danish–Israeli research team has recently reviewed the conflicting results of research on the relation between SOC and physical health. They concluded that the SOC concept is in fact likely to be a valid theory of health, but that its 'operationalisation' – the SOC scale – is technically biased so as to measure mostly the psychological and emotional dimensions of health (Flensborg-Madsen et al. 2005 i and ii).

Since it was launched, the SOC theory has become a well-known concep-

[10] Since the aetiology of cardiovascular disease is discussed in this thesis, it is worth mentioning that a relation was found between dyslipidemia and low sense of coherence in the women's health study in Lund, Sweden. (See Svartvik L et al. Scand J Prim Health Care 2000;18:177-182.)

tual framework in relation to population health. The clinical relevance of focusing on individual people's health-related resources, not only their disease-related risks, is also receiving increasing attention among general practitioners. In 1989, Canadian professor of family medicine Ian McWhinney wrote (McWhinney 1989):

> As family physicians, interested in health as well as diseases, we should also think in terms of factors that increase host resistance and strengthen resistance against noxious stimuli.

More recently, professors of general practice Hanne Hollnagel (Denmark) and Kirsti Malterud (Norway) have made important academic contributions to this developing field (Hollnagel and Malterud 2000). Hanne Hollnagel has also, alongside several other researchers, documented that an individual's subjective evaluation of his or her health is a strong predictor of survival – measured by 'hard' mortality data, for instance, in the field of coronary heart disease (see Møller et al. 1996). We cannot know, however, whether confidence in one's own good health leads to good health by itself, or whether a person who later becomes sick has an inkling at an early stage making him or her predict an unfavourable course. The studies about self-assessed global health, however, indicate that lay individuals do have information about their health which cannot (as yet) be elicited by technological surveying of underlying medical conditions and risk factors (see, for instance, Idler and Benyamini 1999; Hollnagel and Malterud 2000; Bardage et al. 2001; Heidrich et al. 2002; Benjamins et al. 2004).

2.1.3 Van Hooft's framework on subjectivity and health

One final, comprehensive conceptualisation of human health and disease will be outlined here. It departs from the notion of human *subjectivity*. This analytical framework is developed by Australian philosopher Stan van Hooft[11] (van Hooft 1997). He departs from the previously mentioned philosopher Heidegger, who perceives that humans are the only beings for whom *being* is an issue. Van Hooft writes:

> The fundamental, primordial, and inchoate impetus that undergirds human life is the drive towards being, towards "realising" ourselves and our possibilities. Subjectivity is this impetus. The mode of being that we participate in as human beings is that of striving and seeking, struggling and willing (...) fulfilling our potential.

[11] I am grateful to Associate Professor of General Practice in Bergen Edvin Schei, who introduced van Hooft's thoughts to me.

Van Hooft underlines that our human existential struggle should not be seen as a purely mental or emotional phenomenon; it also involves our bodies. At this point, he leans to the arguments of French philosopher Merleau-Ponty who sees *our bodies as the very expression of this quest*. With this is mind, van Hooft finds it helpful to elaborate a model of human subjectivity comprising four levels of functioning. The model is to be understood in a dynamic, not in a hierarchical, sense:

1. *The biological level, i.e., the level of the organism*: This involves a socio-biological "will to live"; van Hooft perceives weeds breaking through the concrete of a car park as a clear example of this. At this level we find the most basic and intrinsic of the subjective values, survival.
2. *The relational level*. This is the level of cognitive and affective reaction to the world around us. At this level, a pre-conscious structuring of the world takes place. We recognise things for what they are, respond to them, and make esthetical judgements. At this level, we can experience the value and joy of being alive.
3. *The pragmatical level*. This involves consciousness in the fully self-aware form, allowing us to think, consider and plan how we can meet our needs and fulfil our desires. At this level we seek explanations for the phenomena we see and the things that happen, and we solve problems.
4. *The integrative level*. This involves our human primordial need to find meaning in our lives, expressed in beliefs and commitments that are central to our integrity and sense of self. At this level we have moral and religious beliefs; we search for pure knowledge and invest in a shared culture. When it comes to appreciating human health and illness, van Hooft sees this fourth level of subjectivity as not only the most distinctive but also the most neglected, in the context of the Western healthcare system.

Whatever we experience as human beings will have significance at all levels. Thereby, a person's ideals, practical goals, comforts and successful bodily functioning are all *equally intrinsic health values*.

Van Hooft claims that the concepts of *disease* and *illness* can be mapped onto his model in a fairly straightforward way. This means that the conceptual framework on subjectivity can be linked up to the biomedical paradigm which addresses health from the perspective of biological

functioning. Biomedical *disease*, understood as organic imbalance/dysfunction, enters at level one of van Hooft's model. Subjective *illness* enters at level two. At this point, van Hooft refers to US philosopher Drew Leder who describes how the body 'disappears' in health and re-emerges as a problem in illness. Van Hooft formulates this in the following way:

> Whereas in health our awareness flows through our body, as it were, without hindrance, and on to the things and people in the world with which we are practically concerned, in illness, the flow of our agency is interrupted and hindered, if not stopped altogether, by our bodily condition.

I personally see another advantage of van Hooft's model of health as subjectivity: it provides analytical space for important medical evidence that does not currently fit under the term 'evidence based medicine'. If we want to be truly scientific in the human domain, we must also strive to include under this term 'evidence' about the particular individual's psychosocial and cultural environment and biography (Engel 1997). Van Hooft's model thereby points in the direction of George Engel's *bio-psycho-social* medical model (Engel 1980, see chapter 2.2.6). This approach is often presented as an ideal, holistic approach. Despite Engel's good intentions, however, the concepts, theories and knowledge from biomedicine, psychology and sociology do not fit into one coherent theoretical framework. It can thereby be hard to apply the bio-psycho-social model in clinical reasoning and decision-making.

2.1.4 Situatedness, embodiment and health

A common theme in the five sub-studies in this thesis is that preventive medicine is becoming increasingly fragmented, decontextualised, and – as a consequence – dehumanised. In accordance with the teachings of scholars, such as George Engel, Ian McWhinney, Drew Leder (1990 and 1992), Eric Cassell (1993 and 1997), Anna Luise Kirkengen (2001), Kirsti Malterud (2002) and sociologist Dorte E. Gannik (2005), I am nevertheless convinced that an individual's *social and cultural situatedness* is highly relevant when it comes to predicting health outcomes. This can be demonstrated by way of 'hard' biomedical endpoints, such as mortality and morbidity, as well as in the distribution of 'surrogate' end points, such as biological risk factors.[12] Reflecting this evidence, the

[12] A comprehensive list of scientific documentation in this field can be found in Anna Luise Kirkengen's book *Hvordan krenkede barn blir syke voksne* (Kirkengen 2005).

notion of *embodiment* is currently entering the vocabulary of epidemiology, as a conceptual tool to facilitate scientific reasoning around the fact that human beings are *simultaneously* social beings and biological organisms. In the words of Harvard Professor Nancy Krieger, embodiment "insists on bodies being active and engaged entities."

Krieger explains how the notion of embodiment advances three critical claims (Krieger 2005):

1. bodies tell stories about – and cannot be studied divorced from – the conditions of our existence;[13]
2. bodies tell stories that often – but not always – match people's stated accounts; and
3. bodies tell stories that people cannot or will not tell, either because they are unable to, forbidden to, or choose not to tell.[14]

With reference to the field of surgery, New Zealand physician Grant Gillett claims that conventional biomedical science has fundamental limitations as a scientific paradigm. He writes (2004):

> The discourse of mechanistic natural sciences serves certain purposes and sees people in certain ways. These significations obscure the function of the person as a holistic, subjective, moral and interactive being whose being-with and belonging-to relationships, replete with issues of power and resistance, are vital to their health. Thus, orthodox medical science is partial and accurate in terms of its own agenda but mistaken when it claims exclusivity or priority for the type of knowledge in which it trades.

According to a similar chain of arguments, Jonathan Mann – physician, the first director of WHO's Global Programme on AIDS, and founder of Harvard University's Center for Health and Human Rights – outlined *human dignity as a crucial element of health*[15] (see Mann 1998; his thoughts were later reviewed by Richard Horton in 2004). Mann categorised four

[13] This might be exemplified by one epidemiological study which illuminates the impact of existential situatedness, although not explicitly saying so: In Denmark it has been found that the death of a child was associated with an overall increased mortality both from natural and unnatural causes in the bereaved mothers between the 10th and 18th year of follow-up. The cause of maternal death was usually unrelated to the cause of the child's death, so an inherited biological susceptibility is unlikely to suffice as an explanation (Li et al. 2003).

[14] This is the topic of Anna Luise Kirkengen's work *Inscribed Bodies. The impact of childhood sexual abuse* (2001).

[15] Quite a lot has been written about human dignity in medical settings that I will not review here. Mann's thoughts, however, appear to be directly relevant to this thesis.

types of dignity violations: *not being seen; being seen, but only as a member of a group; invasion of personal space*; and *humiliation*. He believed that dignity violations can be understood as reducing human resistance, or the capacity to respond adaptively to external stresses. He thought that our current vocabulary and categories related to health and disease are simply too narrow to recognize the impact of dignity violations on human health. Mann's view was that damage to human dignity may turn out to have serious adverse effects on physical, social, and mental well-being that – from a public health perspective – equals that of the impact of viruses and bacteria. Mann's paper from 1998 closes with the words: "The universe of dignity and health now awaits full discovery, and its Copernicus, Galileo and Newton" (Mann 1998).

In the following, I will point to three major research projects which, from different perspectives and by use of different epidemiological approaches, document the relation between social and relational situatedness, on the one hand, and health status (measured in terms of biomedical endpoints), on the other. Each of the projects has resulted in a series of high-quality scientific papers (see Medline or the respective project websites).

i. *A negative health impact of social deprivation, social inequalities, and holding an inferior position in a social hierarchy* has repeatedly been documented, after controlling for known confounding factors. The impact of social situatedness has repeatedly been documented in the Whitehall studies, in particular, *the Whitehall II Study* (http://www.ucl.ac.uk/whitehallII/), which was set up to address this topic specifically.[16] Leading Whitehall epidemiologist Sir Michael Marmot has written much on the subject of *social inequalities and health*.[17] An excerpt from a radio interview in 2002 summarises the findings of the Whitehall studies as well as Marmot's reflections on them:[18]

[16] The 'Whitehall II' study originated from the first Whitehall study of 18,000 men in the UK Civil Service, set up in 1967. 'Whitehall I' showed that men in the lowest employment grades were much more likely to die prematurely than men in the highest grades. 'Whitehall II' started in 1985 and was set up to determine what underlies the social gradient in death and disease and to include women. As before, the study population consisted of administrative employees. The appendix on cardiovascular disease contains references to some of the publications of the Whitehall II Study.

[17] A paper on the links between social processes and human physiology is Marmot MG. *Understanding social inequalities in health*. Persp Biol Med 2003; 46 (3 Suppl): S9-S23.

[18] Sir Michael Marmot interviewed by Robert Paterson: Conversations with History; Institute of International Studies, UC Berkeley, 2002.
http://radio.weblogs.com/0107127/stories/2003/01/26/marmotOnHierarchywhitehall.html

> The lower you were in the hierarchy, the higher the risk. (…) it applied to all the major causes of death – to cardiovascular disease, to gastrointestinal disease, to renal disease, to stroke, to accidental and violent deaths, to cancers that were not related to smoking as well as cancers that were related to smoking – all the major causes of death. (…) Human values, I think, are absolutely crucial here. But I'm also interested in empirical demonstration of how they translate into pathology, because in the end people go and get sick, and a value sounds like something rather abstract – that it's the mind, where, in fact, what happens in the mind has a crucial impact on what happens in the rest of the body. The mind is part of our biological makeup as well. So the empirical study is how the sets of values translate into people's perception of reality, and that, in turn, changes physiology and leads to risk of disease. So we're trying to deal in a crude way with a mind/body question of how the one translates into the other. (...) the whole idea that lack of control over your life, lack of opportunity to participate socially in a meaningful way, could affect whole societies, not just people, depending on where they were within the gradient within a society, was really rather powerful. It suggested that the way we ought to think about health policy should change.

An interesting, emerging concept, which may help us understand and explore the link between situatedness and health, is *allostasis*, meaning "maintaining stability through change." This refers to adaptive physiological processes through which organisms actively adjust to both predictable and unpredictable challenges or threats, including social conflict. Secretion of glucocorticosteroids and activity of other mediators of allostasis, such as the autonomic nervous system, CNS neurotransmitters, and inflammatory cytokines, wax and wane with allostatic load. Serious pathophysiology has been shown to occur if chronic allostatic overload is not relieved (McEwen and Wingfield 2003). Chronic overproduction of cortisol can lead to several destructive paths due to the inadequate regulation of glucose and lipids, resulting in obesity, increased blood pressure, glucose intolerance, and bone mineral loss. Here we might find a key for making sense of studies documenting intriguing associations between severe diseases: linking severity of arthritis to the degree of bone loss independently of steroid-medication; linking low mineral density to high levels of anxiety and depression; linking phobic anxiety and panic attacks to coronary heart disease and sudden cardiac death; linking osteoporosis to atherosclerosis; linking depression and inflammation to coronary heart disease; linking metabolic syndrome to inflammation and dementia; linking sexual abuse experience to hypertension, hyperlipidemia, obesity, and abdominal adiposity; and linking lifetime violation experience to low socioeconomic status and early onset of menopause (see further the presentation and references in Kirkengen 2005).

ii. In accordance with the above-mentioned findings, it has been found that racism and other forms of systematic social discrimination appear to have both direct (psycho-physiological) and indirect (unfavourable life style, poorer access to health care) detrimental effects on health (McKenzie 2003). The direct effects of racism – such as increase in blood pressure among people experiencing degrading treatment but rarely having an opportunity to challenge it – has been specifically addressed by the U.S. *Coronary Artery Risk Development in Young Adults (CARDIA) Study*,[19] (see www.cardia.dopm.uab.edu/index.htm). Another US study from 2004 estimated that elimination of racial disparities in the US was likely to save more lives than any global attempt to perfect the technology of care throughout the healthcare system – first and foremost by reducing what is perceived to be a preventable excess of mortality among African Americans (Woolf et al. 2004).

iii. The third and final project I will mention in relation to situatedness and existential life premises is the US *Adverse Childhood Experiences (ACE) study*.[20] The ACE study indicates that adverse childhood experiences are major risk factors for the leading causes of disease and death as well as for poor subjective quality of life in the United States (Goodwin and Stein 2004).

In this study, the so-called *ACE Score* is used to assess the total amount of certain kinds of stress during childhood. Seven categories of adverse childhood experiences were studied: psychological, physical, or sexual abuse; violence against mother; or living with household members who were substance abusers, mentally ill or suicidal, or ever imprisoned. The number of categories of these adverse childhood experiences was then compared to measures of adult risk behaviour, health status, and disease. Logistic regression was used to adjust for effects of demographic factors on the association between the cumulative number of categories of childhood exposures (range: 0–7) and risk factors for the leading causes of death in adult life (Felitti et al. 1998).

[19] The CARDIA study examines how heart disease develops in adults. It was initiated in 1986 with a group of 5115 black and white men and women, aged 18-30. The CARDIA study is funded by the US National Heart, Lung, and Blood Institute of the National Institutes of Health.

[20] The Adverse Childhood Experiences (ACE) Study is a collaboration between the Center for Disease Control and Prevention in Atlanta and Kaiser Permanente's (KP) Health Appraisal Clinic in San Diego. Over 17,000 KP members underwent a comprehensive physical examination between 1995-1997 and provided detailed information about their childhood experiences of abuse, neglect, and family dysfunction. To date, over 30 scientific articles have been published from the study.

It has demonstrated that as the number of ACE increase, the risk for the following health problems increases in a strong and graded fashion:

- alcoholism and alcohol abuse
- illicit drug use
- smoking
- chronic obstructive pulmonary disease (COPD)
- ischemic heart disease (IHD)
- liver disease
- risk of intimate partner violence
- multiple sexual partners
- sexually transmitted diseases (STDs)
- unintended pregnancies
- fetal death
- health-related quality of life
- depression
- suicide attempts

It has also been found that as the number of ACE increases, the number of co-occurring or "co-morbid" conditions increases (see http://www.cdc.gov/nccdphp/ace/index.htm). In 2002, Vincent J. Felitti, internist and one of the two leading ACE study researchers, summarised the project's findings in these words (Felitti et al. 1998 and 2002):

> The ACE Study reveals a powerful relation between our emotional experiences as children and our adult emotional health, physical health, and major causes of mortality in the United States. Moreover, the time factors in the study make it clear that time does not heal some of the adverse experiences we found so common in the childhoods of a large population of middle-aged, middle-class Americans. (…) What do these findings mean for medical practice and for society? Clearly, we have shown that adverse childhood experiences are both common and destructive. This combination makes them one of the most important, if not the most important, determinants of the health and well-being of the [US] nation. Unfortunately, these problems are both painful to recognize and difficult to cope with. Most physicians would far rather deal with traditional organic disease. Certainly, it is easier to do so, but that approach also leads to troubling treatment failure and to the frustration of expensive diagnostic quandaries where everything is ruled out but nothing is ruled in.

2.1.5 The health benefits of a narrative

Before closing this brief introduction to the nature and origins of health, I will mention the concepts of *narrative-based medicine* and *psychoneuroimmunology*. Narrative-based medicine has recently become a well-established term in the medical vocabulary (Greenhalgh and Hurwitz 1998 and 1999; Greenhalgh 1999; Charon 2004), but its fundamental implications are seldom discussed in the everyday clinical reality I have experienced.[21] Patients' personal narratives of illness provide a framework for

[21] The reason for this is probably linked to the lack of clarity of the concept patient-centred medicine, which I will come to later: Since we are as doctors trained to interpret all information (words, symptoms and findings) within a biologically defined frame, we have never learnt to discern and conceptualise how a patient's story of illness can be regarded as embedded in a meaningful context where the breakdown of health, and/or the person's experience of suffering may often become understandable.

approaching their problems more adequately than the biomedical model does in isolation. The stories provide meaning, context and perspective on the patient's predicament. The narrative approach may help a clinician who has been taught and trained in it, address existential qualities, such as inner hurt, despair, hope, grief and moral pain, which frequently accompany, and may even constitute, peoples' illness. Listening carefully – with an open and prepared mind – to the patient's story, what is being said and how, and what is not being said, may thereby uncover diagnostic and therapeutic options that would otherwise be missed (Greenhalgh and Hurwitz 1999). I realise that I am now touching upon an important as well as controversial topic that has hardly been acknowledged and explored scientifically in medicine. I am speaking of what might be called *existential logic* and the kind of medical reasoning which German-Norwegian physician and researcher Anna Luise Kirkengen has described in her seminal work *Inscribed bodies* (Kirkengen 2001). I will not go further into the issue of narrative-based medicine here; the point I want to make is that there appears to be a growing scientific and clinical awareness that a doctor attending seriously to the patient's story is more likely to facilitate problem-solving, healing and maturation than a doctor who does not truly listen (Frank 1995 and 1998).

It has been empirically documented in various contexts that the process of constructing a coherent story, orally or in writing, entails objective health benefits. That this 'making of meaning' also manifests itself and can be measured on a biochemical level, has been shown by researchers in the field of psychoneuroimmunology (Pennebaker 2000; Fleshner and Laudenslager 2004; Glaser 2005). This fact indirectly validates Antonovsky's previously mentioned theory that experiencing a sense of coherence in one's life is linked to health, all the way down to the level of cellular biology. There is in my mind no doubt that *the process of establishing a sense of meaning, where a person could previously see only apparently fragmented and meaningless events or experiences, involves healing potential*. However, this does not make much sense in the current biomedical model of man (Bateson and Bateson 1987; Ekeland 1997 and 1999; Moerman and Jonas 2002). Since UK professor of general practice Trisha Greenhalgh presented an overview of current knowledge in the field of *writing as therapy* in 1999, 'therapeutic writing' appears to have become a widely established therapeutic tool. But as far as I know, it is rarely used in general medical settings.

The main reason that I want to introduce the topics of narrative based medicine and psychoneuroimmunology here is that I am concerned that medicine tends to ignore the scientific knowledge we already have about the impact of emotions and relations on physiology. This is something I address in all the papers in this thesis, from various angles: In paper I, I discuss the potential impact of maternal distress on the biological development of the child-to-be; Papers II, IV and V consider the links between emotional well-being, self-image, and cardiovascular disease; and Paper III addresses the question of whether an increasing doctors' agenda may eventually divert the dialogue between patient and doctor from other topics of fundamental relevance to the patient's health and potential for healing. My concern is that we might be throwing the baby out with the bath water here: the rapid introduction of new technologies into the consultation invites us to ignore the fundamentally important link between human relations and health. If we do not really listen to what the patients have to say, not only do we deprive them of the rewarding and facilitating experience of being seen and respected for who they are, but we also turn our backs on the medical fact that human relations appear to have healing potential, as well as a potential for inflicting harm, all the way down to a biological level.

2.2 The nature of medical knowledge and 'evidence'

Medicine presents itself as a science-based practice, with the moral aim to relieve human suffering caused by disease (See Paper III; Cassell 1997; Heath and Sweeney 2005). Its activities embrace both the treatment of disease when it occurs, and efforts to protect individuals from predictable disease. Both these enterprises, however, are informed by a conceptualisation of disease, based on *a model of knowledge that is normative for the natural sciences* (Gillett 2004). According to the Western professional medical tradition, i.e., *biomedicine*, this knowledge refers to *an objective and universal description of nature which is thought to exist independent of the observer* (Malterud 2002).

2.2.1 Mainstream biomedical research

Orthodox medical science has, in spirit at least, aimed to follow the Hippocratic healing ethos and model of science aiming at gaining knowledge from *the systematic appraisal of careful and cumulative experience in the domain of clinical practice* (see Appendix 2). However, given what many scholars see as intrinsic authoritative powers attached to academic and

institutionalised medicine, medical science has become bound in a highly positivistic[22] theoretical mode. Consequently, knowledge gained according to the methods of the natural sciences has a tendency to occupy "the epistemic high ground." (see for instance Malterud 2001; Dean 2004).

In the biomedical research paradigm, experimental design is considered the 'golden standard' for obtaining evidence (see for instance Gordon 1988; Cassell 1997; Hetlevik 2004). Furthermore, amongst experimental studies, there is also *a hierarchy of truths*: Observational studies, where "free-living subjects" are investigated in their natural settings, are generally considered a lower form of research inquiry than experimental studies on subjects that have been allocated to experimental and control groups. Also, the application of methodologies other than those of the natural sciences is regarded as inferior and even more unreliable. Thus, philosophical analysis, critical theory, humanistic psychology, sociology and historical investigations are regarded as soft or optional approaches, whilst 'real medicine' lies in anatomy, physiology, biochemistry and statistical method (Gillet 2004).

Correspondingly, medical scientists are used to making a distinction between 'hard' and 'soft' data. This terminology usually implies a judgement about their relative value. From an epistemological viewpoint, however, this involves the comparison of two categories of data that are not comparable. Data from the natural sciences are about *the world of the senses*; whilst data from the human sciences are about *the world of meaning*. What doctors are accustomed to calling scientific knowledge is knowledge of abstractions, whilst hermeneutical[23] knowledge is knowledge of concrete experience as it is lived through. Both types of data can be verified, but the means of verification are different (McWhinney 1989). Many scholars currently believe that quantitative and qualitative research methods need to be more systematically integrated for medicine to make progress (see for instance Malterud 2001).

[22] Somewhat simplified, positivist science regards a human being as a complex biomechanical system whose attributes can be objectively measured in such a way that these measurements define reality. Because it assumes that there exists a uniquely correct or most basic representation of reality, the positivistic view tends to exclude alternative conceptualisations. A distinction between knowledge which is derived from empirical observations and abstract concepts is one of the two central dogmas of positivistic science. The other is reductionism. These two dogmas have come to establish a split between abstract reasoning and empirical observation, and the positivist model holds that certain knowledge can be obtained only from observations made by experimental research (Gillett 2004).

[23] Hermeneutical stems from the Greek *hermEneuein*, which means to interpret.

2.2.2 Is medical progress stagnating?

"Knowledge is power". The saying comes from Francis Bacon (1561-1626), one of the central thinkers of the *Scientific revolution* (see Appendix 2). Bacon believed that knowledge contained the power to conquer man's vulnerable and helpless natural condition[24] (Zaner 2003:161 and 199). The period after 1940 was characterised by a remarkable "medical therapeutic revolution" which can, in a sense, be seen as unleashing dormant therapeutical potential contained within the enormous amount of biomedical knowledge that was collected in the centuries around and after Bacon (see Appendix 2). The rapid and remarkably varied sequence of breakthroughs characterising *the rise of modern medicine* in the second half of the 21st century has been adeptly presented by physician-writer James le Fanu in his 1999 book *The Rise and Fall of Modern Medicine* (le Fanu 1999). As indicated in the book's title, however, le Fanu perceives that medical therapeutical progress has stagnated since the 1980s. His list of major breakthroughs ends in 1984, when a young Australian physician turned medical dogma on its head[25] and proved that *Helicobater pylori* is a chief cause of peptic ulcers.

Historically, every scientific discipline has gone through its golden periods. Twentieth century physics, to take one example, went through an era of major scientific breakthroughs, followed by a relative decline, seen in relation to its funding. Several scholars believe that biomedical progress is currently halting in a similar (relative) fashion (see for instance Murphy 1997; le Fanu 1999; Gillett 2004; Dean 2004; Charlton and Andras 2005; Deyo and Patrick 2005) [26]. They believe that progress is currently inhibited by a "mass cultural belief in medical breakthroughs" among the medical profession and note that although contemporary research is conducted on an ever more impressive scale, it has a tendency to represent "more of the same."[27] As an example of this type of argument, I

[24] Norwegian philosopher Hans Skjervheim addresses this positivistic conception of knowledge as an instrument to predict and control our surroundings, in his essay *Tillit til vitskapen og tillit til mennesket* (See Skjerveim 2002).

[25] When Barry Marshall (b. 1951, Nobel Prize laureate 2005) submitted an abstract about *H. pylori* to the annual meeting of the Australian Gastroenterology Association in 1983, it was rejected (www.medscape.com/viewarticle/514219_1).

[26] To give an example, the total investments in biomedical research in the USA rose from 37.1 billion dollars in 1994 to 94.3 billion dollars in 2003. This represents a doubling when adjusted for inflation. Moses H et al. *Financial anatomy of biomedical research*. JAMA 2005;294:1333-42.

[27] The ever increasing size of research projects addressing cardiovascular disease risk and prevention is illuminated in the historical time-line in Appendix 4.

will mention a paper titled *Life on the exponential curve – time to rattle the academic cage?*, by UK general practitioner David Kernick (2005). He believes that current biomedical research on medical interventions operates "on the flat of the curve" and thereby yields marginal returns in terms of improved health care delivery. He states that while "clinicians have kept their heads down", in recent years the academic/researcher community has been busy "developing unworkable solutions in a voluminous literature that few read", based on (Kernick 2005:2-3):

> models and metaphors that sit within a positivist approach. Research is seen as enhancing prediction and control over a given phenomenon. The focus is on reliability, validity and generalizability. Systems are viewed as linear (there is a simple relationship between inputs and outputs), reductionist (a system can be understood by breaking it down into its component parts) and deterministic (a knowledge of the component parts will predict the future). Research is an objective, value-free and essentially technical process through which researchers reveal or discover knowledge that can be made explicit. The truth is out there. All that is needed is more studies and bigger research grants.

The previously mentioned *Goals of medicine project group* described this in 1996 in terms of "the expansive, ambitious, open-ended pursuit of progress – the battles against illness that are never quite won – that has been the mark of medicine over the past 50 years [and] may now have reached the boundaries of perceived affordability in many countries" (Callahan 1996:S4). Referring to the military metaphors so prevalent in medicine, a US specialist in cancer epidemiology warns that "search and destroy" attitudes are not necessarily the optimal strategy for enhancement of public health (Welch 2005).

Paper V in this thesis illustrates how a large-scale, recent European project addressing the complex problem of cardiovascular disease (CVD) from the traditional and simplified perspective of conventional risk factors, can be seen as contributing little that is new to our understanding of and ability to tackle this problem. The main implication of the most recent (2003) European guidelines on CVD prevention in clinical practice (DeBacker et al 2003), on which papers IV and V in this thesis focus,[28] is that there is "evidence that the majority of the Europeans should take their future risk for cardiovascular disease seriously" (Lindberg 2005). It has however been known for decades that CVD is the main cause of

[28] The findings of papers IV and V have been verified in two other studies published in October 2005 (Neuhauser et al. 2005, Hartz et al. 2005), as will be outlined in the discussion chapter.

death in Europe. Nevertheless, for some unknown reason, the size of the 'high risk' group that should receive maximal clinical attention according to the guidelines, must have come as a surprise to the guideline authors. In a letter submitted to the *BMJ* in July 2005, they stated that the high-risk group would represent "a small proportion" of European populations.[29] On the other hand, we should not forget that CVD mortality rates have declined steadily in Western Europe during the last 30 years (see figures in chapter 3.2), and that from an overall perspective, some of the so-called CVD 'high-risk regions' (including Norway) exhibit populations that are among the world's longest- and healthiest-living, according to WHO statistics.

2.2.3 The biomedical disease model and its limitations

In her seminal text *Tenacious assumptions in Western medicine*, US medical anthropologist Deborah Gordon documents that biomedical thinking has developed in close interplay with Western culture and society-at-large (Gordon 1988). In accordance with Thomas Kuhn (Kuhn 1962; see also Appendix 2), Gordon argues that our preconceptions of what should be regarded as 'correct' ways of obtaining knowledge are heavily influenced by socially constructed tenets and beliefs. Those are in turn rooted in Western philosophy, in particular the canons of the scientific revolution and the Enlightenment. Appendix 2 contains a series of notes on the historical development of modern medical reasoning, from the times of antiquity to the foundations of the reductionistic, biomedical paradigm as we know it today, established in the beginning of the 1900s.

The value-laden foundation of biomedical theory is rarely acknowledged within the medical community. It is widely maintained that medical *facts* represent a morally neutral description of reality. In a paper called *Reflexivity and metapositions* (2002), Kirsti Malterud emphasises

[29] In a rapid response to a BMJ editorial about Paper IV of this thesis by Westin & Heath, the authors of the 2003 European guidelines wrote: "Finally, if our Norwegian colleagues (Getz et al.) have identified an appreciable proportion of their population with less than ideal serum cholesterol and blood pressure levels, they should be congratulated for identifying an opportunity to further improve the health of their people. This could be achieved through reinforcing existing public health messages with regard to nutrition, weight, exercise and smoking for these, the vast majority of who will be healthy. For the small proportion that already have established vascular disease or are at very high multifactorial risk, more intensive advice and evidence based drug therapies might be required". (See the Rapid response by Graham IM, de Backer G and Pyörälä K following Westin S, Heath I. *Thresholds for normal blood pressure and serum cholesterol*. BMJ 2005;330:1461–1462. Access through www.bmj.com).

that healthcare professionals have to acknowledge their *situated positions as 'knowers'*. She writes:

> Potential biases affect the way in which evidence is gathered and used. When clinicians are not committed to appraising the evidence constituting the foundations of their enterprise, quality assessment of clinical practice becomes causal and unreliable. (…) Evidence-based medicine in the original sense requires that doctors reflect upon their own positions as knowers, in the process of situated knowing, where certain rhetorical spaces[30] rule.

Along the same lines, US professor emeritus of sociology Renée C. Fox claims that authors of medical textbooks often emphasise that doctors need *cultural competence* in order to deliver effective clinical care. However, she claims "such authors almost invariably fail to recognize that their own [medical] culture also merits enlightened examination, for it is far from a neutral background against which other cultures may be measured" (Fox 2005). As has been pointed out, for instance by Malterud, every clinician and medical researcher is trained, socialised and situated in a professional culture[31] rendering him or her far from equally attentive to all types of scientific 'evidence'. In the minds of most medical professionals, medical knowledge gathered from the perspective of the natural sciences, systematically ranks higher in clinical practice than other kinds of knowledge in a hierarchy of what is considered relevant (Gordon 1988; Malterud 2001 and 2002). Some aspects of the particular culture pertaining to the fetal medicine expert community when I investigated that area is outlined in Paper I of this thesis.

2.2.4 How medical doctors think – reflections by McWhinney and Cassell

Doctors come to individual clinical encounters with a basic 'biomedical knowledge and preconception kit' guiding their work. Canadian professor of family medicine Ian McWhinney has adeptly summarised this 'biomedical way of thinking' as follows (McWhinney 1989):

> Patients suffer from diseases which can be categorised in the same way as other natural phenomena. A disease can be viewed independently from the person who is suffering from it and from his or her social context. Mental and physical diseases can be considered separately, with provision for a group of psychosomatic diseases

[30] The concept 'rhetorical space' refers to social locations whose tacit rules structure and limit what can be said, with a reasonable expectation of being heard, understood and taken seriously. In these spaces, certain utterances are not acknowledged, not because they are false, but because of power-induced practices that disqualify certain speakers. See Malterud (2002).

[31] Psychiatrist and medical anthropologist Arthur Kleinman speaks of "the biomedical culture."

> in which mind appears to act on the body. Each disease has a specific causal agent[32] and it is a major objective of research to discover them. Given a certain level of host resistance, the occurrence of disease can be explained as a result of exposure to a pathogenic agent.[33] The physician's main task is to diagnose the patient's disease and to prescribe a specific remedy aimed at resolving the cause or relieving the symptoms. (...) The physician is usually a detached observer and the patient a passive recipient in this process.

Appendix 2 in this thesis presents some historical, philosophical and methodological milestones, which, according to my understanding, lead up to this particular way of reasoning about disease and suffering. A medical model conceptualising the human body *as nature* can obviously be adequate in many instances, and it has sufficed to solve many technical challenges in medicine. As a general theory of human health and disease, it is however *not scientific enough*, in my opinion. It does not allow the clinician to develop what Malterud calls the 'fresh clinical knowledge' needed to solve the problems of *particular patients* as they are encountered in daily practice (Malterud 2002; Kirkengen 2002).

In one of his most influential books, *Doctoring – the nature of primary care medicine* (1997), US physician and clinical emeritus professor of public health Eric J. Cassell draws up a picture of the "medical paradigm" similar to that of McWhinney. Cassell then draws the following conclusion (1997:46):

> The belief that medicine involves the application of impersonal acts to an objective problem that can be seen separately from the person who has it, is the cardinal and emblematic error of twentieth-century medicine.

Cassell's observations related to primary health care include:

> Many of the functions we want primary care physicians to perform do not logically follow from or are contradicted by medical science as it is taught to students (1997:44).

> Knowledge of the particular patient is, in fact, necessarily the exact opposite of scientific knowledge (1997:45).

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[32] Note by LG: The causal agent may be for instance a gene, a biochemical or neurophysiological aberration, or a microbe. In 2006 it appears correct to presume that several causal agents may interact, but everyday clinical reasoning in relation to causality is nevertheless simple, linear, and in accordance with McWhinney's argument.

[33] Note by LG: In the context of the germ theory, virulence is defined as the relative capacity of an infectious agent to overcome host defences. Research has focused far more on disease agents than on host defences or the interaction among biological, psychological and social influences that are involved in the protection and

> The only instrument that can come close to knowing a person is another person (1997:45).

I would like all papers in this thesis to be read in light of these observations, which I believe we have to consider seriously.

2.2.5 Call for new approaches: complexity of science and syndemiology
As previously mentioned, linear reasoning related to conventional biomedical risk factors has come to dominate research in preventive medicine. The risk concept as such, and the methods used to investigate risks and outcomes, are, however, rarely scrutinized (Taubes 1995). One basic problem is that these methods rely on risk ratios relating exposure to outcome, with no elaboration of intervening pathways. Biological risk markers, however, are rarely ultimate causes. Rather, they are outcome variables resulting from interactions between other variables. It may thus represent a rather crude scientific approach to act upon risk factors in isolation.[34] Furthermore, the factors predicting health in a given population are not necessarily the best predictors of health for individuals (Rose 1985; Poortinga 2005). There is therefore increasing interest, also among epidemiological researchers, to develop more sophisticated scientific methods to address the major health problems of our times (Taubes 1995; Arnetz 1996; Dean 2004; Gatrell 2005).

During the last 5-6 years, the terms complexity, non-linearity and dynamic systems have appeared ever more frequently in the scientific literature (Mikulecky 2001). This can be exemplified by a series of papers in the British Medical Journal in 2001 (among these: Wilson et al. 2001; Plsek and Greenhalgh 2001; Fraser og Greenhalgh 2001), as well as papers in several other influential scientific journals, such as Social Science and Medicine (Mechanic 1995; Gatrell 2005). Complexity can apparently be understood in various ways. Anthony Gatrell at the Institute of Health Research in Lancaster, UK, writes (2005):

> Complexity is about relationships that cannot be reduced to simple linear models or their variants (such as logistic regression).

He goes on to say:

[34] Simple risk algorithms (as described in paper V) can be seen as included in this critique of 'crude' scientific approaches.

> If one lesson has emerged from the spectacular failure of Western medicine to eradicate certain diseases, it is that diseases cannot be reduced to a single cause or explained within a prevailing linear scientific method: complexity is their hallmark.

Another recent scientific concept, in many ways related to complexity theory, is syndemiology. Syndemiology refers to the fact that many risk factors are "not merely concurrent, not wholly separable, but closely linked and interdependent threats to health and well-being" (Singer and Clair 2003). The 'syndemic' approach first arose as a method to model the emergence and uncontrollable spread of global epidemics of infectious disease, such as AIDS and drug-resistant tuberculosis. Syndemiology currently appears to gain more general attention among experts of public health (Gerberding 2005). As previously outlined, there is an increasing body of evidence that all the major health problems in contemporary societies are closely interwoven with potent societal enhancers, such as social disparity, child abuse and neglect, discrimination, poverty and structural violence (Farmer 2005; Mustillo et al. 2004).[35]

2.2.6 Objectivity critique and the patient-centred clinical method

Drew Leder is perhaps the philosopher of medicine who has most elegantly formulated what Cassell called "the emblematic error" of modern medicine. In 1990, he wrote (Leder 1990):

> In seeking to escape all interpretative subjectivity, medicine has threatened to expunge its primary subject – the living, experiencing patient.

[35] An example of syndemiology: The increased morbidity and mortality among people reporting adverse childhood experiences, including sexual abuse, is well documented (see the presentation of the ACE study in chapter 2.1.4). It is, however, a great methodological challenge to conceptualise, investigate, and suggest adequate preventive measures related to the various causal "webs" that may underlie this relation. Several examples of 'syndemic reasoning' can be found in Anna Luise Kirkengen's works. Here is one (Kirkengen 2005:160): Persons who report having experienced sexual abuse in childhood/adolescence tend to lead more unstable and 'unhealthy' lives, including smoking, alcohol and drug use, compared with persons with no such experience. Statistically, abuse is also linked to an earlier sexual debut, more partners and more unprotected sex – which increases the risk for sexually transmitted disease, including Human Papilloma Virus (HPV) infection. HPV is a central causal factor in the development of cancer of the cervix. It is also known that smoking has biological effects directly increasing the carcinogenic potential of HPV infection. Furthermore, it is known that chronic detrimental emotional stress, more often present in people with a history of abuse than among others, leads to allostatic overload (overactivity of the hypophysis-pituitary-adrenal axis). Allostatic overload appears to reduce the human immune system's cellular defence against cancer development. It is also documented that women with a history of abuse are more reluctant to undergo gynaecological examinations than other women. They are thus overrepresented among the non-participants in cervical cancer screening programmes. This increases the risk that their cancer will be detected at a later stage, with a worse prognosis.

Swedish general practitioner and researcher Carl Edvard Rudebeck has expressed similar concerns, i.e., he perceives that the doctor's awareness of the possible *disease* is often more immediate than his or her awareness of the *person* sitting opposite him in the consultation room (Rudebeck 2000).

In scientific disciplines other than medicine, including physics, theory of science, anthropology, sociology or linguistics, the notions 'factual truth' and 'scientific objectivity' gradually lost their meaning after the Second World War (see Meland et al. 2000). In Norway, the most eminent representative of this so-called objectivity critique was philosopher Hans Skjervheim (1926-1999). The question of what a human being is, and is not, runs through Skjervheim's works, which contain a general and eloquent critique of the claims of objectivity in philosophy, the sciences, and the science-based professions.[36]

In France, the birthplace of the *scientifically based clinical method* as we know it in Western biomedicine around 1820 (see Appendix 2), Michel Foucault later came to present a critical analysis of the striving for objectivism in medicine. In 1963, he first published a renowned book, titled *The Birth of the Clinic. An archaeology of medical perception* (Foucault 1975). Foucault's aim is to demonstrate how much of what we think of today as 'pure science' is, in fact, owed to social and cultural trends and attitudes, such as the climate of the French Revolution and Paris hospital medicine.

Foucault notes how becoming a patient means becoming vulnerable and involves a diminution of social and political status. He links this to a concept which he calls "power/knowledge" (see Milchman and Rosenberg 2003). He describes how medical doctors have developed a particular discourse where speech (French: parole) and observation (surveillance) collapse into one act: the gaze (regard). The gaze involves an act of objectification. This concept, "le regard médical" – better known in English as "the medical gaze" – is situated at the core of Foucault's teachings about medicine. He himself introduced The birth of the clinic as a book about "the act of seeing, the gaze." Among the essential statements in this book, is:

[36] Skjervheim's essay *Det instrumentalistiske mistaket* (The instrumental mistake), first published in 1972, is probably his best-known contribution to the 'objectivity critique' in Norway. The essay can be found in Skjervheim's book *Mennesket* (2002).

> The clinical gaze is a gaze that burns things to their furthest truths (p. 120).

The historical roots of the medical gaze are outlined in Appendix 2.[37] According to Foucault, the all-seeing medical gaze – revealing what is considered to be the simple, scientific truth[38] – can also come to function as an instrument of professional control, what he calls *a disciplinary technology*. He described this as "a policy of coercions that act upon the body, a calculated manipulation of its elements, its gestures, its behaviour." He noted that "the human body was entering a machinery of power that explores it, breaks it downs and rearranges it" (Milchman and Rosenberg 2003:63). In his works, Foucault investigated the concrete historical developments of techniques related to organization, administration, surveillance, examination and documentation in medicine (as well as other contexts) and demonstrated an increasing emphasis on 'normalization' and 'standardization' of populations as time went by.

According to Foucault, the medical gaze not only had an impact on medical practice; it has also came to construct society's general view of a wide range of phenomena. The labels 'health' and 'illness' can serve as remarkable de-politicizers of an issue. By focusing the source and treatment of problems on the individual, other levels of understanding and intervention are effectively closed. Furthermore, by defining something as an illness, the issue becomes not *whether* it is desirable and defendable to deal with the problem, but rather *how* and *when*. Foucault described a 'medicine of the species', which involves diagnosis and treatment of disease, making the individual body an object for observation and treatment by the medical profession. However, referring to prevention, he also described a 'medicine of social spaces', where public health is subjected to regulation by the state.

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[37] As an example of how Foucault worked, he used historical material containing scientific descriptions of phenomena relating to the human body as nature developed in a highly selective way. Lacking a perceptual base, early medical observations (Foucault uses an example from 1769) appeared in what he calls "a language of fantasy." But gradually, as a result of the meticulous investigations in pathology and physiology, these descriptions attained a distinctly new quality. By the early 1800s (Foucault gives an example from 1825), the reader's attention is directed into "a world of constant visibility" (the gaze). Medical science had thereby established the tradition for describing medical facts in terms of patho-anatomical descriptions – as we still know them today.

[38] Martin Heidegger made a major point of the transition from the Greek to the Roman perception of 'truth' and noted that this represented a decisive event in the history of Western countries. The Greek word was *a-letheia* (unconcealment, a rather open and creative concept), whilst the Romans introduced the word *veritas* (meaning "the correspondence of matter to knowledge"), which was a strict and calculative, one might say technologically oriented, concept. See Milchman and Rosenberg 2003.

Mainstream medical research and practice was never profoundly affected by the objectivity critique put forward by Foucault and other thinkers. Scottish psychiatrist Ronald Laing (1927-89) can however be mentioned as an exception to this rule. Influenced by the existential philosophers, Laing wrote several books, including *The Politics of Experience* (1967). It contains a profound critique of medicine's affection for the concept of *normality* in relation to the human state and behaviour. Concerns that the biomedical paradigm – useful as it may be in many circumstances – ultimately represents a de-humanised way of looking at the human condition also came to generate concern among ambitious and academically oriented doctors in the field of primary health care, most notably in Great Britain and Canada. During the 1950s, psychoanalyst Michael Balint worked with groups of British general practitioners to explore the nature of the doctor-patient relationship. Balint was struck by the inadequacies of the conventional method for reaching what he called *a deep understanding* of the patient's illness (Balint 1964). Michael Balint is said to have been the first scholar to apply the term *patient-centred medicine*[39] (Meland, Schei et al. 2000). Balint also introduced other analytical concepts, such as *attentive listening* and *the drug doctor* – the latter referring to the physician as a powerful diagnostic and therapeutic 'tool'. This choice of perspective again highlighted the importance of *self-knowledge* in the physician.

Inspired by objectivity critique and *systems theory*,[40] psychoanalytically trained internist George L. Engel presented the previously mentioned *bio-psycho-social model of illness* in the late 1970s (Engel 1977 and 1980). The model received considerable attention, and Engel's teachings are still widely honoured in the medical curriculum. Nevertheless, as previously outlined, bio-psycho-social approaches, such as the discourse on 'human situatedness' have not as yet come to influence medicine in any fundamental sense. Philosopher Drew Leder has pointed

[39] A similar trend took place in clinical psychology in the 1950s, as Carl Rogers developed a method called person-centred therapy. In the essay *Om mentorskap og medisin* (Getz 2004), I have reflected on my own clinical experience in light of Rogers' person-centred method. Norwegian general practitioner and researcher John Nessa also writes about the Rogerian tradition in his book *Medisin og eksistens* (2003).

[40] In the second half of the 21st century, systems theory was launched in response to the limitations of 19th-century science. It was apparent that the mechanistic worldview and reductive methods of this approach were unable to deal adequately with organic phenomena like organisation and growth. Reductionistic method deals with problems by cutting them down to size, separating them from their surroundings and reducing them as far as possible to simple, linear, causal chains. Systems theory seeks to do the opposite, i.e., to approach problems by considering all their significant *relationships*.

out that bio-psycho-social medical practice is no easy task. He explains how "Cartesian dualism has fractured the language of the self" (Leder 1998:128), and, in fact, we do not have any consistent medical theory to direct a "bio-psycho-social" clinical approach. More than a decade after he launched his model, Engel described the current state of affairs in medical research as follows (1992):

> The exclusion of nonmaterial human phenomena mandated by medical science's continuing allegiance to a 17th century scientific world view has constituted a major obstacle to medicine's scientific maturation as a human discipline. But 20th century conceptual changes even in physics (not to mention the influence of the theory of evolution) now renders that exclusion untenable and in effect legitimizes efforts to devise scientific means appropriate for the human domain.

Around this time, Ian WcWhinney at McMaster University presented his *patient-centred clinical method* (Levenstein et al. 1986; McWhinney 1989). His *Textbook of family medicine* rapidly became a classic, having a strong impact on general practice ideology, particularly in Canada, the UK and the Nordic countries. McWhinney writes that his ideas and clinical approaches are directly influenced by the works of Balint, Engel, and also those of Harvard psychiatrist and Professor of anthropology Arthur Kleinman.[41] McWhinney describes *the patient-centred clinical method* in the following manner:

> Its essence is the physician's attempts to fulfil a twofold task: understanding the patient and understanding the disease. From this understanding flows the management of both patient and disease (1989:111).

> In practicing the patient-centered clinical method, the physician attaches equal importance to following the traditional medical agenda and to understanding the meaning the illness has for the patient. This involves understanding the patient's expectations, feelings, and fears. Reaching this understanding should be an objective in every clinical encounter (1989:118).

Since the concept *patient-centred medicine* was launched, referrals to "patient-centred clinical care" have spread rapidly throughout medicine. The term is currently a word of honour in major policy documents, issued by, for instance, WHO.[42] There is, however, still no formal con-

[41] Among Kleinman's renowned works are *Patients and Healers in the Context of Culture* (1981) and *The Illness Narratives: Suffering, Healing, and the Human Condition* (1988).

[42] One example is a WHO document titled *Preparing a health care workforce for the 21st century. The challenge of chronic conditions* (2005). The first among five core competencies listed as essential for health care workers to have, is the ability to "provide patient-centred care".

sensus among scholars as to exactly what patient-centered clinical practice encompasses (Mead and Bower 2000). Most writers appear to agree that, in essence, patient-centred care acknowledges the *patient as a person with a unique life-history and needs*, and that patient-centred interactions can be seen as "those in which the patient's point of view is actively sought by the physician" (Zandbelt 2005). The concept of patient-centeredness, however, appears to have different connotations to different scholars when going into specific detail. Researchers trying to operationalise and measure the phenomenon of patient centeredness in an 'objective' manner, evidently face a scientific challenge. Zandbelt (2005) has summed up research on the effects of patient-centeredness on clinical practice. Not unexpectedly, the results have been contradictory. Some researchers have found that patient-centred communication promotes a positive relationship between doctor and patient and enhances patients' recall of received information, adherence to medication and satisfaction and also their 'objective' state of health. Other studies have found no or even a *negative* relationship between "patient-centeredness" and health outcomes, patients' satisfaction and doctors' satisfaction. The reason for these apparent contradictions is most likely that patient-centeredness has been operationalised and evaluated differently in different studies. There is indeed an old adage which says "whoever sets the frame, sets the game."

The inherent tension between 'doctor-centred' and 'patient-centred' medical care is an implicit or explicit topic in all the five papers in this thesis. It is most explicitly addressed in Papers II and III, which describe how a humanistically oriented primary care clinician, striving to take the patient's agenda seriously and also wishing to apply medical evidence which does not pertain to the narrow paradigm of *evidence-based medicine* (EBM), can face fundamental ethical dilemmas. This is because the tradition of EBM has come to define the current 'golden standard' for what healthcare personnel, in general, and doctors, in particular, should be occupied with, and for what should be regarded as relevant and important in the clinical encounter (Hetlevik 2004). To put it another way, EBM has, as I see it, come to demarcate the scientific arena within which the individual patient is invited to exercise his or her autonomy and right to make 'informed choices'.

2.2.7 Evidence-based medicine

The first Medline citation of "Evidence based medicine" (EBM) appeared in 1992. In 2004, the number of citations numbered more than 13 000 (Straus 2004). Several visionary and enthusiastic individuals contributed to the foundations of EBM. Among them were Archie Cochrane (key word: summarising of evidence), Alvan Feinstein (defining principles of quantitative clinical reasoning) and David Sackett who, together with a team of close co-workers at McMaster University in Canada, contributed tremendously influential innovations in relation to teaching of bedside critical appraisal skills (Sackett et al. 1997).

As far as I can judge the intentions of the researchers and clinicians founding EBM, they were driven by a strong sense of professional responsibility to avoid inflicting harm on patients (Ashcroft 2004). In its original formulation, EBM can be said to have begun as a radical and anti-authoritarian grass-roots movement aiming to counteract the detrimental influence of unsystematic clinical experience, biased expert reviews, and uncritical use of pathophysiological rationale[43] as a basis for clinical interventions. EBM aimed at helping practicing clinicians evaluate the best available medical evidence in relation to therapeutical interventions. EBM should thus 'empower' individual clinicians to stand up to authorities and develop independent views regarding medical claims and controversies.

In the introduction to the textbook *How to practice and teach evidence based medicine* (1997), David Sackett and co-workers explain what EBM is:

> Evidence based medicine, whose philosophical origins extend back to mid-19th century Paris and earlier,[44] is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.

One of the most cited accounts of EBM is the following (Sackett, Rosenberg et al 1996):

[43] An example of harmful application of pathophysiological rationale: It was presumed that suppression of ventricular arrhythmias in patients who have suffered a myocardial infarction would reduce their subsequent risk of death due to arrhythmia. The CAST study, however, documented that patients who were treated with antiarrythmica had a 2.5-fold increase in mortality, compared with the placebo group (Rogers WJ et al. N Engl J Med 1989;321:406-12). At the peak of their use in the late 1980s, it has been estimated that anti-arrhythmic drugs caused 20.000-70.000 premature deaths per year in the US alone (Peter Götzsche, Nordic Cochrane Centre, pers. comm., 2003).

[44] The roots of EBM can however hardly be called philosophical; their nature is rather methodological.

> The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence. By individual clinical expertise, we mean the proficiency and judgement that individual clinicians acquire through clinical experience and clinical practice.

The wish to dismantle the tradition of expert-based, authoritarian medicine is apparent in a humoristic paper by David Sackett in the *BMJ* (2000), where he publicly resigned from an academic position which he found quite intolerable. During the previous decade, he had paradoxically risen to the position as "an expert on EBM"! He thereby claimed that, in spite of EBM's democratic intentions, "there are still far more experts around than is healthy." Ironically enough, it appears that EBM, which was intended to help clinicians think for themselves, had been appropriated by the very expert community that it was designed to challenge. Describing his experiences of being considered an expert, Sackett wrote:

> Whether at a meeting or in print, I was always given the last word on the matter. It then dawned on me that experts like me commit two sins that retard the advance of science and harm the young. Firstly, adding our prestige to our opinions gives the latter far greater persuasive power than they deserve on scientific grounds alone. Whether through deference, fear, or respect, others tend not to challenge them, and progress towards the truth is impaired in the presence of an expert. The second sin of expertness is committed on grant applications and manuscripts that challenge the current expert consensus. Reviewers face the unavoidable temptation to accept or reject new evidence and ideas, not on the basis of their scientific merit, but on the extent to which they agree or disagree with the public positions taken by experts on these matters. (...) new ideas and new investigators are thwarted by experts, and progress toward the truth is slowed. (...) Two clinical signs confirmed that I was once again an expert. The first was the reception of an honorary degree and the second bears my name: "Sackettisation," defined as "the artificial linkage of a publication to the evidence- based medicine movement in order to improve sales"."

All the papers in this thesis confirm that even at the height of the EBM era (where we currently may find ourselves), Sackett still has a point. Authoritative expert opinion is currently issued, but now in the name of EBM. The 2003 European guidelines on cardiovascular disease prevention in clinical practice may be seen as an illustrative example, as discussed in papers IV and V. I have previously written that in relation to prenatal screening and diagnosis, practicing clinicians are wise to remain reflective instead of adhering uncritically to recommendations from the authoritative expert community (Getz 2001 ii). After having prepared

papers IV and V in this thesis, I have come to believe that similar scepticism is also warranted in relation to the claims of CVD experts.

Since it was launched, the concept of EBM has been widely appraised, debated and criticised, in both the medical and the philosophical literature. In his book *Ethics and evidence-based medicine. Fallibility and responsibility in clinical science* (2003), Kenneth W. Goodman notes that EBM has:

> …reshaped medicine and other health professions, even as they have been subjected to vigorous and vehement criticism. The growth of evidence-based medicine has occurred against a backdrop of health care reform (…) cost containment and quality improvement, and clinicians have been urged to adopt the rigours of science whilst remaining true to their "clinical judgement". This tension – between efforts to make medical practice more scientific and the suspicions of many clinicians – has caused one of the greatest practical and ethical challenges in the history of the health professions.

According to my knowledge of the literature, the original group of EBM proponents has, from the beginning, emphasised the limitations of using evidence alone (as contained within the paradigm of EBM) to make treatment decisions. This group acknowledges that values and preference judgements are implicit and important in every clinical management decision. Thus, they have defined *clinical expertise* as (Guyatt et al. 2004):

> the ability to integrate research evidence and patients' circumstances and preferences to help patients arrive at optimal decisions.

EBM proponents do not, however, seem to problematise the theoretical foundations of EBM as such; they perceive that the main challenge of the future is to get EBM out to all its potential users:

> EBM's biggest future challenge is one of knowledge translation, ensuring that clinicians base their day to day decision making on the right principles and on current best evidence. All too often clinicians are unaware of the available evidence or fail to apply it.

From an epistemological point of view, there may however be other and more fundamental challenges facing EBM (Ashcroft 2004). These challenges relate to the limitations of the scientific paradigm of EBM. A heated debate on the strengths and limitations of EBM has taken place

in the scientific literature ever since the concept was launched.[45] On one side, there are scholars believing that the epistemological flaws of EBM are so severe as to be regarded as fatal for the paradigm (see Cohen 2004). On the other are scholars believing that EBM has limitations that can and should be resolved through methodological refinement. The polarity of this debate is reflected in a paper by Greenhalgh who asks: "Evidence based medicine – objective science or intellectual imperialism?" (Greenhalgh 2002). The epistemological limitations of EBM are a central theme in all the papers in this thesis.

What seems to be common among 'evidence-based' approaches to decision making is not only the adherence to epidemiological methods but a tendency to emphasise, and even exaggerate, the division between the empirical world of 'facts' and the social world of meaning and values. The wish to separate medical facts from human values, however, does not capture the complex relationship between empirical analysis, moral discourse, and truth/reality or right action. There is obviously much more to 'scientific' decision-making than using the results of epidemiological surveys and randomised trials (Petros 2003).

The ethical debate surrounding EBM can be confusing at times. This is partly because arguments belonging to different levels and domains of the subject tend to be mixed (Gerber and Lauterbach 2005). To take one example, opponents of EBM claim that "EBM endangers therapeutic freedom". At the same time, proponents of EBM claim that the "doctor's autonomy is greatly reinforced by EBM". Both arguments can in fact be seen as important and defendable, depending on the context.[46] In this thesis, however, I put more emphasis on the epistemological weaknesses of the EBM paradigm than on its obvious strengths.

[45] Since 1997 *The Journal of Evaluation in Clinical Practice* has featured a yearly theme issue on "the evidence-based healthcare debate," by the journal's editor-in-chief, Professor of Public Health Sciences A. Miles and co-workers. These issues give an overview of the evolution of the EBM critique. The journal expressed strong criticism of the EBM nomenclature in 1997-1998, commenting on its "rhetorical world-play", "unscientific and antiscientific nature" and "pseudo-authoritative presentation". Later, as EBM has been "put into 'its place' as a technique of significant but limited utility within modern medicine" (as the authors worded it in 1999), there has been emphasis on further developing the underlying philosophy of evidence-based health care and scrutinising various scientific, clinical and ethical challenges that are raised by the paradigm of EBM.

[46] The same apparent "liberating-confining paradox" has been described in relation to *medical technology in general*. In his paper *The paradox of health care* (2001), Bjørn Hofmann notes that "Although health care technology might be conceived to increase the possibilities of the professionals, it appears to make them a slave of their tool. Where it should increase [the health care worker's] autonomy, it appears to restrict (his) action. New advanced technology enforces [health care workers] to act according to its application procedures. Instead of being liberating and facilitating, (…) technology appears to be confining."

In 2004, a categorisation of common critical arguments in relation to EBM was presented by Aaron M. Cohen and co-workers at the Department of Medical Informatics and Clinical Epidemiology in Oregon (2004). Their overview will be briefly outlined below. I have added some typical quotations and arguments from other publications to illustrate each of Cohen's five themes.

1. *Too much emphasis on empirism.* Example: "Medical doctors claim that their discipline is founded on scientific knowledge. Yet, although the ideas of evidence based medicine are widely accepted, clinical decisions and methods of patient care are based on much more than just results of controlled experiments" (Malterud 2001).
2. *Too narrow a definition of evidence.* Example: In 2002, Trisha Greenhalgh noted that EBM favours evidence that is gathered through randomised controlled trials and epidemiological studies on the course of disease, at the cost of other relevant evidence, such as philosophical and ethical, physiological, economical, contextual, psychological and organisational evidence.
3. *EBM lacks evidence of efficacy, meaning that the assumptions of EBM are not in themselves evidence based.* Examples: "Strangely, the evidence of the central claim, that EBM will improve patient care, is conspicuously absent" (Norman 1999). "Its [EBM's] most basic assumptions are unproved, indeed largely untested. (…) Good science is not the sole determinant of the right things to do. (…) Many of us teach EBM (integrating best evidence with clinical expertise and patient values), knowing that it is nearly impossible to practice in everyday clinical care" (Reilly 2004). "EBM and the broader forms of evidence-based decision-making it has occasioned raise provocative questions about the relation of scientific knowledge to social action across a variety of domains. Social science inquiry about EBM has not yet reached the scale one might expect, given the breadth and significance of the phenomenon" (Mykhalovskiy and Weir 2004).
4. *EBM has limited value and relevance in relation to individual patients, as it relies entirely on statistical means that are derived from groups.* This can be illustrated by a recent qualitative study showing that health professionals in British general practice report perceiving that EBM has a tendency to create "a myth of certainty around what is inherently uncertain" for the individual (Griffiths et al. 2005). A reflection upon this dilemma can also be found in Bjørn Hofmann's paper *The*

paradox of health care (2001). Hofmann writes: "The methods of modern health care are based on abstracting general knowledge from specific cases and applying this knowledge for particular patients. On the one hand, the individual patient only has a statistical significance; on the other hand, he means everything. In generating health care knowledge, he is only a number, in the application of knowledge, however, he is the application's aim and its legitimacy. A precondition for statistical health is to ignore the individual.[47] Through such generalisations, health care became science, by seeing the general in the particular, it was able to establish reproducible results" (Hofmann 2001:377). The dilemmas linked to application of data representing a mathemathical representation of a non-existent 'average' human being (epidemiological data) to a particular and unique human being have also been highlighted by Kirkengen (2005) and Hetlevik (2005).

5. *EBM represents a threat to the autonomy of the doctor and/or a threat to the doctor-patient relationship:* "As medicine is essentially 'work in progress', how do we foster a healthy tension between doctors' autonomy and 'standard of care' (…) The art of medicine is slowly eroded by treatment protocols" (Genuis and Genuis 2004). Along with other scholars (such as May et al. 2006), I believe there is a strong ideological tension between EBM and the narrative-based approach. A qualitative study from British general practice sheds light on this matter. It is one of several studies that have investigated why general practitioners (GPs) show limited adherence to preventive medical guidelines, even in relation to individuals who can be considered as at high risk for primary or secondary disease events (this general phenomenon is addressed in Papers II-V in this thesis). Its title introduces the project's main conclusion in a thought-provoking manner: *'I saw the panic rise in her eyes, and evidence-based medicine went out of the door. An exploratory qualitative study of the barriers to secondary prevention in the management of coronary heart disease'* (Summerskill and Pope 2002). The investigators sum up the study as follows: "The doctor-patient relationship may act as a barrier to the delivery of secondary prevention in primary care." They appear to respect this finding and immediately suggest that evidence should perhaps rather be implemented by healthcare workers other than the GPs. They suggest delegating the task of "opportunistic and GP-led secondary prevention to nurse-led protocol-driven clinics,"

[47] Comment by LG: At this point, it may be relevant to point out that one of the four categories of previously mentioned Jonathan Mann's classifications of human dignity violations involves that of being seen as a member of a group only (Mann 1998; elaborated in Horton 2004).

as "this strategy would avoid forcing GPs to choose between 'evidence' and what they see as important and valid aspects of patient care, such as responding to patient anxiety, or nurturing long-term professional relationships with their patients." Personally, I think that when evidence that is thought to represent "the best of medical science" is relatively often perceived as incompatible with maintaining the doctor-patient relationship in everyday practice, it is also important to scrutinize the 'ethos' of this evidence.

All papers in this thesis investigate the above-mentioned problematic areas of the EBM approach, with reference to everyday clinical practice reality.

2.3 Conceptualising medical ethics

Medicine is a professional moral enterprise with the ultimate aim of helping people. Many elements of our medical, professional, ethical code go back to the times of Hippocrates (400 B.C). The strong and circumscribed discipline called bioethics[48] is, however, a very recent phenomenon which has emerged during the last three decades. Quite unfortunately, this discipline has however become a separate academic field, dominated by scholars with limited or no clinical experience. It has thereby come to live a life of its own, as a "whole industry of experts on good and evil" in the words of Edvin Schei.[49] It tends to favour eye-catching dilemmas that are usually quite far from the everyday problems which practicing clinicians face in areas such as primary health care. Nancy Scheper-Hughes, US professor of anthropology, WHO advisor and director of Organs Watch, therefore speaks of "armchair bioethicists [who] can ignore the real world and its messy social, economic, cultural and psychological realities. They only need to conjure up a hypothetical world…". [50] It may also be a concern that within the relatively separate academic field of bioethics, narrow subspecialties are currently emerging. As stated by researcher Stephan L. Chorover at the Massachusetts Institute of Technology, ethical subspecialisation is emerging as an un-

[48] Merriam-Webster's dictionary: Ethic: from Latin *ethice*, from Greek *EthikE*, from *Ethikos* 1: the discipline dealing with what is good and bad and with moral duty and obligation. 2 a: a set of moral principles or values b: a theory or system of moral values <the present-day materialistic *ethic*> c: the principles of conduct governing an individual or a group <professional *ethics*> d: a guiding philosophy.

[49] Schei E. *Goodness – what is it in medicine*. Lecture at Rosendal seminar 2005.

[50] Scheper-Hughes N. *The ultimate commodity*. Lancet 2005;366:1349-50.

acknowledged ethical dilemma in relation to cutting-edge, hi-tech biomedical research, such as neuro-imaging (Chorover 2005).[51]

The societal environment in which medicine is being practiced is currently undergoing rapid and dramatic changes, in terms of ideology, organisation and financing (Potter and McKinlay 2005). These changing premises for the delivery of care form the point of departure for the 5th edition of the *Ethics Manual* that was recently issued by the American College of Physicians (Snyder et al. 2005). One of the explicit aims of the manual is to "shed light on how existing [ethical] principles extend to emerging concerns." The *Ethics Manual* opens with the following statement:

> Medicine, law and social values are not static. Reexamining the tenets of medical practice and their application in new circumstances is a necessary exercise.

Papers I-V in this thesis deal with ethical issues that arise in – or relate directly to – primary health care, under the influence of increasing scientific reductionism and implementation of new medical technologies.

2.3.1 Principlistic American bioethics and its shortcomings

Contemporary clinical-medical ethics is heavily influenced by the four so-called "Anglo-American principles" that were developed in the USA in the 1970s. It is important to realise that this approach emerged in a very particular cultural context (Tauber 2001). It should also be seen in light of unethical experiments on American human 'guinea-pigs', conducted in the 1950s and 60s,[52] experiments that were even sponsored by official medical bodies (Skrabanek 1990).

The four principles of the US ethical paradigm are: *respect for patient autonomy, nonmaleficence, beneficence* and *justice* (Beachamp and Childress 1979). The "principlistic approach" is not grounded in any

[51] Neuro-ethics is related to studies of how our mental and behavioural manifestations (i.e., our thoughts, feelings and actions) depend on neural conditions, i.e., brain physiology and biochemistry. Chorover writes: "To make neuroethics a new speciality with its own cadre of ostensible experts is to narrow the discussion of ethical issues and to make the whole subject of social responsibilities of physicians, scientists, and engineers less accessible to the public." In the introduction to her Norwegian book [*How abused children become unhealthy adults*] (2005), Anna Luise Kirkengen also addresses the issue of neuroethics, in a dialogue with Norwegian Professor of philosophy Arne Johan Vetlesen.

[52] Despite the Nuremberg Code (1948) and the Declaration of Helsinki (1964), there were several scandals in the US in the 1950s and 60s, such as the Tuskegee experiment on the natural course of untreated syphilis. Another experiment involved the injection of live cancer cells into the blood stream of mentally disabled persons, etc. The policy of informed consent was enforced in the US *Belmont Report* in 1978. Source: Mann J et al. (eds.). *Health and Human rights.* NY: Routledge, 1999 (p. 363).

comprehensive theory of ethics, but its roots are clearly to be found in the complex moral philosophy of the Western world, with its emphasis on *rationality, independence, objectivity and equality*. In daily life, this principlistic approach represents a practical, methodological guide to ethical discussion and decision-making. Using the four principles and weighing them against each other, clinicians (sometimes with, most often without, explicit guidance from consulting bioethicists) are encouraged to find solutions to the ethical dilemmas they face. Recent experience shows that when principles compete, *autonomy* comes to rank as the super-principle (as will be outlined later in this chapter).

During the last decade, many scholars have expressed concern over the limitations of "the four principles approach". In particular, a lot has been written about the limitations of the principle of autonomy, understood as "an individual's freedom to make his/her personal diagnostic and therapeutic choices" (see, for instance, Donchin 2001; Tauber 2001 and 2003; Callahan 2003; Frank 2004). Critics, such as the so-called *communitarian* thinkers[53], underline that no human being should be regarded as a self-sufficient, independent atom in the world. People always depend on each other and on the society they live in. It appears to be quite common for doctors to perceive that offering a medical test is something that automatically enhances human autonomy. For instance, this view appears to underlie, undebated as such, the foundation of screening programs for fetal anomalies (Parens and Asch et al. 2000). This can be illustrated by a letter by prenatal medicine world authority Kypros Nicolaides, titled *Having the test gives parents options* (1998). The discourse on patient autonomy may however come to divert our attention from the need to scrutinise *the tacit systems of values into which individual "autonomous" choices are embedded*. (Marteau and Drake 1995; Press and Browner 1995; Dunne and Warren 1998). Many researchers have shown how societal and cultural power issues frame and restrict people's private choices (see for instance Donchin 2001; Palmblad 2003, and several philosophical essays in the book *Meaning and medicine*, edited by Lindeman Nelson and Lindeman Nelson in 1999). Prenatal diagnosis is a prime example of a clinical activity which is heavily, and reciprocally, influenced by cultural factors. The obvious limitations of the concept of autonomy in such a context are highlighted in Paper I. I have previously

[53] Examples of philosophers that can be described as communitarian are Daniel Callahan and Charles Taylor (both mentioned in this thesis).

mentioned the emergence of evidence-based medicine as a framework which has come to define what is to be considered important and correct in clinical practice. It thereby circumscribes the field within which autonomous medical decisions can be made, and in my opinion, this can be regarded as a violation of autonomy. This phenomenon has particularly been documented in the area of prenatal testing (Press 2000). The tension between a person's right to be treated as a unique individual and the paradigm of EBM, which mainly offers evaluations based on group-based knowledge, is an explicit topic of papers II and III.

Other scholars have pointed out that references to 'patient autonomy', 'patient empowerment' and 'patient control' may instrumentally serve *to avoid confronting one's own professional responsibility in situations that are problematic for medicine* (Salmon and Hall 2003). It has also been shown that referral to patients' freedom to choose for themselves and to patient demands may be a rhetorical tool to advance narrow professional or commercial interests (Harrington 2002). Norwegian scholars Kristin Bakke and Bjørn Hofmann (2005) have come to the conclusion that such mechanisms are likely to explain some of the increasing use – and overuse – of radiological examinations in contemporary medicine.

Eric Cassell believes that the US principlistic approach has contributed to a gradual shift in the nature of the relationship between patient and doctor. This development, as he sees it, has been towards a combination of *patient-centeredness* and *consumerism*. Or, as Cassell sums it up (Cassell 2000):

> …from treating patients to making treatment decisions.

Cassell also believes that the principlistic approach has implicitly and gradually contributed to conveying a general message that it is not the doctor but science and technology, as such, that diagnose, treat and cure disease (Cassell 2000).

To sum up, the critique of the case-oriented US principlistic ethical approach may represent a call for another guiding moral framework of a "higher order" than the four "middle-level" US principles. What seems to be needed is an ethical framework inviting more penetrating questions than the four US principles have traditionally asked, and also taking the issues of human vulnerability and interdependency into account.

2.3.2 Current trends in European bioethics

In contrast to the traditional US paradigm of ethics, interest is currently increasing in what may be called *relational ethics*. Relational ethics acknowledge human situatedness and interrelatedness (Häyry 2003; Häyry 2005; Frank 2004). One proponent of the communitarian tradition is US philosopher David Callahan, who – drawing upon models from ecology – argues that the first questions asked about any ethical problem should focus on its social meaning, implications and context, even in situations where the problem appears to affect one individual only (Callahan 2003).

In the European bioethics and law environment, a new ethical framework is currently under development. Throughout the 1990s, a systematic process of philosophical investigation has taken place (Häyry 2003), and the result is a suggested set of European ethical principles: *patient autonomy, dignity, integrity* and *vulnerability* (Rendtorff 2002). In addition, it is explicitly stated that *these principles are to be promoted within a framework emphasising solidarity, justice and human responsibility*. Furthermore, it is also emphasised that the European principles represent a deliberate change from "a *contractual rights*" claim to a "*protective rights*" claim (Rendtorff 2002). As yet, I am not aware that the European ethical analytical framework has had much influence on bedside ethical deliberations in Europe. In fact, I had not really taken notice of the on-going search for European ethical principles when I wrote the first papers in this thesis. The overall conclusions I draw from the present study are, however, quite coherent with what I perceive to be the current trends in European bioethics.

2.3.3 'True' knowledge and social awareness as crucial dimensions of medical ethics

Norwegian physician and professor of medical ethics Reidun Førde has presented an original and radical view of the nature of medical ethics which is thought-provoking and highly relevant to this thesis (Førde 2003). According to Førde, clinical-medical ethics, which is what most of us think of as 'medical ethics' in daily life (outlined here above), should be considered only as one of *three dimensions of medical ethical reflection.*

Førde believes that *a primary premise for ethically justifiable medical*

practice is that this practice builds on knowledge that is scientifically 'true'. This means that our professional willingness and ability to critically scrutinise the medical knowledge base on which our actions are based is fundamental. All five sub-studies in this thesis address medical-ethical dilemmas belonging to this sphere. As I interpret Førde, we, as professionals, must be ready to acknowledge our fundamental responsibilities to society as 'producers' and implementers of medical knowledge. We must also accept that 'scientific evidence' is always derived from hypotheses that are conceived *within an ideology* – that is, a set of assumptions about the real world, established by previous evidence, by faith, or by both (Hart 2005).

Secondly, Førde sees *the ability to ask critical questions concerning the role of medicine in society* as important. She exemplifies this perspective with the following questions (English translation by LG):

> Is it possible that the healthcare system contributes to the creation of more illness in society? Do our activities – the preventive as well as the curative, our diagnostic methods, as well as our treatments – affect the population's experience of disease and health and ability to cope with diseases and ailments? Medicine's place in society and the ethical implications following from medical choices also become clearly evident when discussing how to prioritise limited resources. What criteria should underlie the decision that people have a right to certain treatments, and why should other areas of activity receive fewer resources? Can medical activity contribute to the maintenance of socio-economical inequalities?

This approach has much in common with what has been called communitarian ethics and social ethics. *Communitarian* ethics focuses on what one may call "the common good" and envisage a society where people are joined in shared pursuit of values and goals, as opposed to ethics focused solely on the individual. David Callahan believes that "serious ethical analysis must take the social implications [of individually based choices and actions] seriously" (Callahan 2003). *Social ethics* can in short be defined as "a reflection of the goodness or badness of social institutions created by men." It "includes reflections of collective values, prevailing views of men and society (…) and consequences for groups of citizens. (…) Social ethics starts from the presumption that our social institutions and the way they are functioning are ultimately submitted to human responsibility" (Pijnenburg 2002:247). It can be argued that the communitarian approach is particularly relevant to a social-ethical approach to health care, because it introduces attention to the overall goals

and uses of medicine and the humaneness or inhumaneness of its social and cultural conditions (Pijnenburg 2002, Callahan 2003). I will revert to this topic in the discussion part of this thesis.

The ethical dilemmas addressed in the five papers of this thesis can definitely be regarded from such a communitarian perspective, considering medicine's responsibilities as a social institution (Pijnenburg and Gordijn 2005).

On her *third and final level* of ethical reasoning, Førde arrives at the more familiar discourse on *clinical-medical ethics*, with its focus on *the interaction between the individual doctor and patient*. Papers I, II and III of this thesis touch directly upon clinical interactions. Papers IV and V address this matter indirectly, as they discuss how clinical guidelines and authoritative clinical recommendations affect the structural *premises* for clinical interaction. The collection of papers in this thesis thereby illustrates that ethical dimensions of Førde's model are in fact closely interconnected: an individual choice cannot be regarded as autonomous unless it is informed by true and comprehensive scientific knowledge (Papers I, II and III). And implementation of new medical knowledge is not ethically defensible unless societal implications of this knowledge have been carefully considered (Papers IV and V).

2.3.4 "Primum non nocere" and "think harm always"

Since the times of Hippocrates, the medical duty of *not inflicting harm on patients* has been emphasised. We are all familiar with the dictum *Primum non nocere* (above all, do no harm). The origin of this Latin phrase is not quite clear, but a recent medical paper attributes it to the teachings of English physician Thomas Sydenham (1624-1689),[54] (Smith 2005).

The Austrian-born polymath, historian, theologian and anti-institutional writer Ivan Illich[55] (1926-2002) is probably the scholar who has drawn most

[54] *Primum non nocere* – sometimes recorded as *primum nil nocere*: It was long regarded to stem from Galen's paraphrasing of a Hippocratic aphorism. Hippocrates taught (in Greek; *Epidemics*, Bk. I, Sect. XI) "to help, or at least to do no harm." One historian believes that use of the phrase in modern times can be traced to Paris hospital medicine (i.e., the cradle of "evidence-based medicine") in the mid-1800s. A recent paper (Smith 2005), however, claims that the axiom first appeared in English, coupled with Latin, around 1860, and attributes it to the teachings of Sydenham (1624-1689). (Source: www.wikipedia.org).

[55] Illich's intellectual activities in the 1970s and 1980s focused on major institutions of the industrialised world. In seven concise, non-academic books he addressed education, technological development, energy, transport and economic development, medicine and work (Source: *Ivan Illich. Obituary*, the Guardian Dec 9, 2002).

attention to the phenomenon of medical harm in recent times. He used the term *iatrogenesis* (originating from physicians) to designate harm induced by medical activity. The first sentence in Illich's seminal book *Limits to medicine. Medical Nemesis. The expropriation of health* (1976) reads:

> The medical establishment has become a major threat to health.

Health, argues Illich, is the capacity to cope with the human reality of death, pain, and sickness. Technology can help, but modern medicine has gone too far, launching into a Godlike battle to eradicate death, pain, and sickness. In doing so, it turns people into consumers or objects, destroying their capacity for health. Illich's key message has several similarities to the teachings of Petr Skrabanek, who said: "Medicine is not about conquering disease and death, but about the alleviation of suffering, minimising harm, smoothing the painful journey of man to the grave. Medicine has no mandate to be meddlesome in the lives of those who do not need it" (Skrabanek 1994:22). The ideas of Illich and Skrabanek have some features in common with the teachings of Foucault and Laing (see chapter 2.2.6) (Nye 2003). And after Illich and Skrabanek, many other writers have addressed similar topics. The critique is often linked to the term *medicalisation* (US language: medicalization).[56] There is quite an extensive literature on this topic, which I will not go into here.[57] The essence of medicalisation has been outlined in the following way: *medical models come to influence standards of pathology and norm, therapeutic philosophies and techniques, strategies for social intervention, and theories of deviance and punishment* (Nye 2003). An example of a working definition, which I believe captures the most common understanding of medicalisation among medical practitioners today, resulted from a seminar held by the Danish Medical Association in 1997[58] (translation by LG): "By medicalization is meant that an

[56] As far as I know, the term medicalisation was coined by medical sociologist IK Zola in 1975.

[57] On April 13th 2002, the British Medical Journal published a theme issue titled *Too much medicine?* which focused on various aspects of medicalisation and also the concept 'disease-mongering'; i.e., attempts by the pharmaceutical industry, aided by medical opinion-leaders, to define human problems as diseases for which there are medical solutions (drugs). In addition, the following two papers may exemplify discussions of medicalisation in concrete clinical contexts: Barker KK. *A ship upon a stormy sea: the medicalization of pregnancy*. Soc Sci Med 1998;47:1067-76. Thomas-MacLean R, Stoppard JM. *Physicians' constructions of depression: inside/outside the boundaries of medicalization.* Health (London) 2004;8:275-93.

[58] See Hvas AC. *Sygeliggjøring og medikalisering. Forsøg på begrepsafklaring på baggrund af en litteraturstudie.* Ugeskr Laeger 1999;161:5783-5: "Ved medikalisering forstås, at større og større dele av menneskelivets reaktioner og livsfaser defineres ud fra en medicinsk forståelsesramme og derved fører til et anliggende for sundhedsvesenet."

ever-increasing part of human reactions and life phases become defined according to a medical frame of understanding, thereby becoming matters to be dealt with by the healthcare system." However, various uses and interpretations of the term medicalisation exist, and it is not automatically a given that medicalisation is a negative thing. It is therefore important to clarify how the concept is to be understood in any given context or debate.

In *Limits to medicine*, Illich described three 'levels' of medically induced harm, which he at the time called *iatrogenesis* (Illich also adopted the term medicalization to cover some of these phenomena, but that was later):[59]

- *Clinical iatrogenesis* is the injury done to patients by ineffective, toxic, and unsafe treatments. Illich believed that 7% of patients suffer injuries while hospitalised. Yet only in the past few years and in a few countries have doctors begun to take patient safety seriously.[60]
- *Social iatrogenesis* results from the medicalisation of life. More and more problems are seen as amenable to medical intervention. Pharmaceutical companies develop expensive treatments for non-diseases. Health care consumes an ever-growing proportion of the budget.
- Worse than all of this for Illich is *cultural iatrogenesis*, the destruction of traditional ways of dealing with and making sense of death, pain, and sickness. "A society's image of death," argues Illich, "reveals the level of independence of its people, their personal relatedness, self reliance, and aliveness". Dying has become the ultimate form of consumer resistance.

On July 3rd 2004, the *British Medical Journal* published a theme issue dedicated to the challenging task of *balancing benefits and harm in health care*, and to exploring "some of the many ways health care might result in harm". In the introduction to that issue, Richard Smith advises medical doctors to consider the potential for inflicting harm *in relation*

[59] This summary is a quote from a review of *Medical Nemesis*, which Richard Smith (editor of the *BMJ* and an admirer of Illich's writings) wrote (Smith 2002).

[60] Illich's critique of clinical iatrogenesis may have appeared harsh and radical to many healthcare workers when it first appeared, but some of his thoughts have become mainstream now. At a leadership seminar at the Landspitali University Hospital where I work, I was recently presented with US data indicating that around 10% of hospitalised patients are likely to experience some kind of detrimental event, caused by medical activity.

to every single intervention, "even a throwaway comment or a test 'just to be sure'." He concludes (Smith 2004):

> Hard and uncomfortable as it may be, we need to think about harm all the time.

Human experience may serve as a point of departure for discussing various aspects of medically induced harm. And in this context, *the human experience of being labelled as at-risk for future disease is central*. All papers in this thesis deal with this topic, approached from various angles. Paper II contains an analysis of a situation where a doctor suspects that s/he might have inflicted unintentional existential harm by the benevolent and plain act of implementing medical evidence in relation to an elderly gentleman who came to get a medical certificate for the renewal of his driver's license. Papers IV and V discuss the consequences of labelling a large majority of the Norwegian population as having an unfavourable biological health profile, or as being at high risk for cardiovascular disease. I will not go deeply into the issue of the human experience of being at-risk, or the psychological costs of screening programmes (along the lines of Stewart-Brown and Farmer 2005), but it is important to recognise that a body of literature addresses this subject from various general perspectives (see, for instance, Ogden 1995; Kenen 1996; Lupton 1999; Reventlow et al. 2001). Some researchers have also addressed this topic in concrete clinical contexts, such as cardiovascular disease (Haynes et al. 1978; Irvine and Logan 1994; Andersen 1998, see ref. 32 in paper II) and evaluations of bone mineral density/osteoporosis among currently healthy women (Hvas et al. 2005). A new Danish qualitative study on women's experience of being labelled as having increased risk for osteoporosis found that technological information about the inner status of the body, until then unacknowledged by the women themselves, left most of them more uncertain and their lives more restricted than before, as opposed to feeling more in control and 'empowered' in face of the future. Along with what has been found in many other studies on health examinations, the women in this study, however, expressed satisfaction with the opportunity to have the bone scan. The authors conclude that it is important to consider the ethics of the use of medical technology to detect asymptomatic risk conditions, as it can induce *a new sense of illness* (Reventlow et al. 2006).

Paper I in this thesis penetrates the particular topic of pregnant women's experience of carrying a fetus categorised as at increased risk for anom-

aly or disability. It also highlights the possibility that maternal existential experience may come to affect fetal development, according to the 'fetal programming hypothesis' which states that fetal environment and maternal experience influences the 'design' of the future individual[61] (Bateson 2001; O'Connor et al. 2005; Van den Bergh et al. 2005).

There are also several other angles from which to consider the issue of medical harm. A recent analysis suggests that there are likely to be twice as many deaths from adverse drug reactions as there are from car accidents in the UK and the US (Pirmohamed et al. 2004). This estimate, along with recent tragedies, such as the detrimental effects of prescribing certain kinds of antiarrythmica (previously outlined in a footnote in chapter 2.2.7 about EBM), uncritical recommendation of hormonal replacement therapy (HRT) among postmenopausal women (a penetrative analysis of the history of HRT is presented by Krieger et al. 2005),[62] and too aggressive marketing of so-called Cox-2 inhibitors, which led to numerous coronary deaths, reminds us that a *precautionary principle* in relation to medical interventions is as important as ever. One lesson to be learned from these events is that, whenever possible, medical intervention trials should be designed to enable assessment of the risks and benefits of interventions with equal scientific rigor (Psaty et al. 2005).

There is increasing concern among radiologists related to the steadily increasing number of procedures involving a high load of radiation, such as computed tomography and invasive radiological interventions. Italian researcher Eugenio Picano points out that the medical sources of radiation in industrialised countries are now exceeding the levels of radiation from natural sources (Picano 2004). He calls for a debate on the sustainability of the current practice in this field. He quotes Illich, who wrote in 1976, at the beginning of "the imaging era":

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[61] This theory originates from the Forsdahl-Barker hypothesis, mentioned in Appendix 4 of this thesis (in the context of cardiovascular disease).

[62] Routine acceptance of the use of hormone replacement therapy (HRT) was shattered in 2002 when results of the largest HRT randomised clinical trial, the women's health initiative, indicated that long-term use of oestrogen plus progestin HRT not only was associated with increased risk of cancer but, contrary to expectations, did not decrease, and may have increased, the risk of cardiovascular disease. In June 2004 a group of historians, epidemiologists, biologists, clinicians, and women's health advocates met to discuss why, and how, for four decades, millions of women were prescribed powerful pharmacological agents already demonstrated to be carcinogenic? Krieger and co-workers conclude that in order to answer this question, one must engage core issues of accountability, complexity, fear of mortality, and the conduct of socially responsible science (Krieger et al. 2005).

> Act so that the effect of your action is compatible with the permanence of genuine human life. Very concretely applied this could mean: Do not raise radiation levels unless you know that this action will not be visited upon your grandchild.

In the context of medical imaging, however, harm is not only a vague possibility that can affect future generations. It can also affect present users. Several researchers have warned that extensive use of CT scanning as part of aggressively marketed, preventive medical programmes,[63] can – by itself – cause a significant increase in the incidence of cancer. A single full body CT of a 45-year-old adult would – referring to the technology in question in 2004 – result in a life-time attributable cancer mortality risk of 0,08%. If this same individual is persuaded to undergo a yearly CT scan for the next 30 years, his or her accrued life-time attributable cancer risk would be 1,9% (Brenner and Elliston 2004). Risk estimates of this kind are needed to assess the utility of medical screening by radiological imaging, both from an individual and public health point of view (Lee et al. 2004; Brenner and Elliston 2004).

The final perspective in my considerations of iatrogenic harm has been brought forward by Ian McWhinney in his textbook (1989), which includes a particular section on harm in relation to preventive medical programmes. Among the potential harms of preventive medicine, McWhinney reflects upon *the meaning of the term normal*. He writes (1989:165):

> In the history of medicine, few errors have led to so much harm as the failure to be precise about the meaning of the term normal. (…) The history of medicine is full of examples of unnecessary suffering imposed on patients because they have been erroneously classified as abnormal.

As examples, McWhinney mentions elaborate bed rest regimens that were wrongfully assigned to young people who had sinus arrhythmia, 'wholesale' removal of large tonsils, and misclassification of mitral valve prolapse as a life-threatening condition. McWhinney also quotes

[63] Particularly in the US, many radiological examinations are currently performed as a result of direct-to-consumer advertising. CT technology is currently advocated to detect atherosclerotic heart disease (EBCT), lung cancer (CT), colon cancer (CTC), as well as for "general screening" (total-body CT). See Ashar BH et al. *Current evidence for the use of emerging radiologic technologies for disease screening.* Am J Manag Care 2005;11:385-92. The paper states that population screening by CT is not as yet supported by evidence, whilst it carries a potential for harm that has yet to be explored in full, involving false positive findings, harmful effects of unnecessary, invasive testing, infliction of worry and concern, false negative findings and radiation doses.

(1989:166) a distinguished doctor named John Ryle who, already in 1946, observed that failure to study the limits of variability has implied that:

> Each new instrument has left a trail of faulty diagnoses in its wake.[64]

Despite technology getting ever more advanced, the problems with defining normality do not seem to have diminished with time. In 1993, Black and Welch wrote a seminal paper about the problem of disease overestimation by use of new diagnostic imaging techniques (1993). Paper I in this thesis documents that life-threatening ethical dilemmas arose in the 1990s as a result of technically induced uncertainties related to the definition of normality.

How can we conceptualise the causes of iatrogenic harm induced by a "lack of careful considerations related to the application of the term abnormal?" McWhinney suggests the following categories:

1. *The distinction between normality and abnormality is regarded as an either/or question*. The use of arbitrarily chosen cut-off points in relation to phenomena which we know are continuously distributed is obviously a problem. Thereby one person with essentially the same blood sugar as another person (just at the other side of an arbitrarily chosen cut-off point) may end up as "having diabetes", whilst the other is classified as "normal". A recent editorial in the *New England Journal of Medicine* highlights the problems of responding to patients' concerns about this issue (Arky 2005). Papers IV and V in this thesis also address this topic.
2. *"The normal is confused with the average"*. McWhinney refers to the practice of considering test results that lie outside two standard deviations from the mean as abnormal. This is the kind of fallacy that led Edmund Murphy, professor of medicine at Johns Hopkins University, to define – quite ironically – a normal person as "one who has been insufficiently investigated".[65]
3. *Criteria of abnormality for a new test may have been arrived at by testing an unrepresentative sample of the population*, such as people admitted to hospital or a particular clinic. Paper I in this thesis illustrates dilemmas related to the application of data from high-risk populations

[64] Ryle refers to the stethoscope, the sphygmomanometer, the gastroscope and various laboratory methods.

[65] Murphy EA. *The logic of medicine*. 1st ed. The Johns Hopkins University Press, 1976.

of pregnant women in low-risk settings. Paper V discusses a similar phenomenon, i.e., the problem of risk overestimation due to 'retrospective risk bias'.

4. *Physicians reflect cultural norms of their own society and social class* and may therefore classify as abnormal or unhealthy human behaviour that should rather be classified as unfashionable or unpopular. Norwegian general practitioner and researcher Janecke Thesen has recently conceptualised, in a more general fashion, how medical doctors can come to show oppressive attitudes in the clinical encounter (Thesen 2004 and 2005).

2.3.5 "Corruptio optimi pessima" and the power(s) of goodness[66]

This chapter's final entry on medical ethics focuses on the issue of concealed power. Ivan Illich frequently cited the Latin maxim corruptio optimi pessima; the corruption of the best is the worst. He was concerned about what he perceived to be corruption of public institutions which, in his opinion, ended up by performing the opposite of their original purpose. He believed that the roots of this process lie in the institutionalisation of charity in the 13th-century church. Along the same lines as Illich, Skrabanek criticised the WHO's definition of health for representing a "medicalisation of man's search for Utopia", which gives the medical establishment a carte blanche to intervene in the private and social spheres of people's lives. This leads into what Skrabanek calls 'coercive altruism', meaning that it becomes possible to *expropriate human health in the name of goodness*: promoting people's health can only be good, therefore one can use all means possible (see also Hofmann's recount of these thoughts in Grimen and Elvbakken (eds.) 2003). Even David Sackett has pointed out that the presumed goodness of such projects makes it very hard to challenge and criticise preventive medical programmes (Sackett 2002).

As previously mentioned, social historian Michel Foucault focused on the constellation of "power/knowledge" and maintained that power/knowledge apparatuses reach "right down into the depths of society", such as medical institutions (Foucault quoted in Milchman and Rosenberg 2003:61). Among Foucault's key messages is that one may be able to identify considerable *power hidden within scientific discourses that are regarded as neutral and 'true'*. As previously mentioned, he saw

[66] This refers to the 2005 Rosendal seminar *The power of goodness* (see methods chapter).

modern science as difficult to separate from *disciplinating* technologies and, in this context, introduced the notion of *biopower* (this is outlined in Reventlow et al. 2006). Foucault was particularly observant of what he perceived to be overlooked consequences of individual or collective practices and programmes. He found that power/knowledge complexes tend to be of a diffuse, deep and often hidden character and was particularly concerned with the *oppressive effects of practices that are generally regarded as beneficial or benign* (Milchman and Rosenberg 2003, Nye 2003). Foucault noted that "power is tolerable only on condition that it masks a substantial part of itself. Its success is proportional to its ability to hide its own mechanisms" (Foucault 1987:86).

It is possible to argue that the constellation of societal mandate and aspiration to scientific truthfulness in the domain of medicine can open the way for direct coercion and exploitation of human beings. Daniel Callahan (2003) believes there is a definite potential for coercion by means of medical technology, without our really recognising what is happening. He writes that "the power of technology and the profit to be made from it, can control and manipulate us even more effectively than authoritarianism. Moral dictators can be seen and overthrown, but technological repression steals up on us, visible but with an innocent countenance." He then explains how he believes that modernity's focus on individualism and autonomy can effectively fuel coercive processes: "Liberal individualism makes this scenario more easily possible, and is why it is not a tolerable guide to the sensible use of medical knowledge and technology" (Callahan 2003:506). Callahan's concerns related to medical coercion by use of medical technology in relation to autonomous subjects, brings to mind a concept that has been outlined by English sociologist David Riches; *tactical pre-emption*. Riches pointed out that the most efficient way of dominating and exploiting people is to make them believe that what is happening is for their own good (Riches 1986, Ehrenreich and English 1979).

At the 2005 Rosendal seminar,[67] Anna Luise Kirkengen reflected upon the "power of goodness". She will have the final word on the ambiguous topic of the power of goodness in medicine:

> Medical goodness, as a construct, in the wrong hands and guided by wrong knowledge or wrong intention, is the most powerful tool for modern colonisation. (…)

[67] Kirkengen AL. *Goodness, risk and responsibility.* Lecture at the Rosendal seminar, 2005.

> Scientifically grounded techno-biomedicine may, in the name of goodness, progress and help, become the worst imperialist ever. Defined as matter and manipulated for the betterment of their owners, so to speak, both human minds and human bodies are about to become unlimitedly exploitable. In the perspectives of the global market, the human body and mind are the new third world. And, remarkably enough, this third world of bodies is to be found in the affluent parts of the old first and second world, Western countries.

To illustrate the relevance of this concern, I would like to mention that the newly established and ambitious open access web journal *Public Library of Science* (PLoS, see www.plos.org) aims to counteract an ever more widespread phenomenon which has been designated *disease mongering*. Disease mongering can be seen as a particular kind of medicalisation (Moynihan and Heath 2002). PLoS is co-organiser of the first conference on disease mongering to be arranged in the world (in April 2006, see www.plos.org/disease-mongering), and the organisers write in the announcement:

> The pharmaceutical industry's drive for innovation, essential for sustaining profitability, has extended beyond the invention of novel drugs to sponsoring the creation of new diseases, disorders and dysfunctions, and the expansion of old ones. Using informal alliances with physician and patient groups, and with help from public relations experts, drug companies now 'brand' conditions, just as they brand medicines.

Whether one believes that medicalisation of human lives is currently beginning to involve elements of exploitation and coercion or not, it is important to realise that modern techno-bio-medicine does indeed involve strong legitimating forces that might function as concealers of hidden power, by way of assuming a kind of a 'cognitive authority' in a Foucauldian sense (Pippin 1999). On the one hand, medicine has *a societal mandate* – extended to a monopoly, and, on the other, it refers to *a scientific framework*, which – as Foucault pointed out – aspires to represent *the truth*. Another theoretical concept coming to mind here is *symbolic capital*, as formulated by French professor of sociology Pierre Bourdieu (1930-2002). Symbolic capital includes such resources as prestige and authority, and – importantly – the legitimate ability to *define situations* (see Dixon-Wood 2006). Correspondingly, Bourdieu speaks of *symbolic power*. This is "the power to impose the legitimate vision of the social world and its divisions" (see Dixon-Woods 2006), or – in Bourdieu's own words – "that invisible power which can be exercised only with the

complicity of those who do not want to know that they are subject to it or even that they themselves exercise it" (Bourdieu 1991:164). Analyses of symbolic capital and power in medicine play a central role in what has been termed "the sociology of bio-ethics" (Dixon-Woods 2006). Here, the links between power and ethical deliberations are being analysed, and close attention is being paid to power relations in ordinary, everyday practice where mind-boggling ethical dilemmas are not evident.

I believe that the issues of symbolic and hidden power have a certain relevance to all papers in this thesis.

2.4 The nature of medical technology

Medical technology is a core concept in this thesis, so it needs to be defined and outlined.[68] This presentation of medical technology and its value-ladenness is strongly influenced by the works of Norwegian scholar Bjørn Hofmann, who has written extensively on medical technology and ethics.

2.4.1 Conceptualising medical technology

Technology can be defined in various ways. *Encyclopædia Britannica* defines it as "the application of scientific knowledge to the practical aims of human life or, as it is sometimes phrased, to the change and manipulation of the human environment." It can also be described as the development and application of tools, machines, materials and processes that help to solve human problems. As a human activity, technology can be seen as predating both science and engineering. It embodies the human knowledge of solving challenges in the design of standard tools, machines, materials and processes. Thus, *standardisation of design* is an essential feature of technology. In daily life, the term technology typically characterises inventions and gadgets using recently-discovered scientific principles and processes. However, it can be argued that even very old inventions, such as the wheel, are examples of technology.

In its original Greek form, the word *techn*E covered the activities and skills of a craftsman, and also the arts of the mind and the fine arts. In this context, technology was seen as a way of bringing forth, of reveal-

[68] The word *technology* originally stems from the Greek *technologia*, meaning systematic treatment of an art, from *techn*E art, skill + *-o-* + *-logia* –logy: a manner of accomplishing a task, especially using technical processes, methods, or knowledge.

ing, the truth. This could be done by manufacturing and manipulating some object by use of instrumental means. But it could also imply the artist's act of bringing forth "the true in the beautiful" by a particular blend of technical skills and mindful contemplation. Bjørn Hofmann has argued that in relation to medicine, the term techne actually integrates the scientific and technical as well as the normative aspects of the activity (Hofmann 2001 iii). In his famous 1953 essay *The question concerning technology*, Martin Heidegger departs from this ancient Greek way of conceptualising *technE as a form of poiesis* (bringing forth) (Heidegger 1977).

In his thesis *The technological invention of disease – On disease, technology and values* (Hofmann 2002:11), Hofmann defines contemporary technology in general, and relates it to medicine in particular, in the following way:

> By technology I understand the complex of devices, methods and organisations applied in human purposive activity. Both in terms of devices, methods and organisation, technology today is integrated in modern medicine. A defibrillator (heart starter) is not just a box with wires, electrodes and electronic components (device). It is a defibrillator on behalf of the methods of medical resuscitation applied in the organisation of health care.

When talking about *medical technology*, it is not unusual to encompass such dissimilar 'things' as drugs, surgical procedures, imaging devices, screening and diagnostic tests, electronic gadgets, lifestyle change protocols and clinical guidelines under the term "medical device". In addition to these instrumental devices come, as Hofmann describes, organisational structures, strategies and other approaches that are designed to achieve defined purposes (Mechanic 2002, Deyo and Patrick 2005). According to US sociologist David Mechanic, the recent transformation of American medicine has resulted as much from changes in what he designates as *social and organisational technologies*, as they have resulted from the use of conventional medical technologies in the form of diagnostic and treatment tools (Mechanic 2002).

In the following chapter, I will outline the clinical contexts that are being addressed in Papers I-V. They are *antenatal screening for fetal anomaly, cardiovascular disease (CVD) prevention*, and *the consultation between doctor and patient in primary health care*. In each of these contexts, one particular type of technology is being addressed: ultrasound imaging, a

CVD risk assessment tool with accompanying guidelines, and a particular body of evidence-based medicine. In chapters 3.1-3.3, these technologies will be defined according to the terms outlined by Hofmann: *device, method* and *organisation*.

2.4.2 Heidegger on technology: Questioning builds a way

The relation between human beings and technology is a vast and complicated philosophical topic. It is beyond the scope of this thesis to examine the literature dealing with "the philosophy of technology." Among the prominent philosophers who have contemplated this topic are the previously mentioned philosophers Martin Heidegger (1889-1976)[69] and his students Hans-Georg Gadamer (1900-2002) and Hans Jonas (1903-1993). Heidegger is generally considered one of the most influential[70] and controversial European philosophers of the 21st century. In his essay *The Question Concerning Technology* Heidegger stated that:

> The essence of technology is by no means anything technological.

What he meant is that the essence of technology is *existential*, that is, how human beings, in their social practices, are primarily oriented in the world as knowing subjects (Milchman and Rosenberg 2003). He thereby warned against an 'instrumental' understanding of technology as simply a set of tools "to get things done". According to Heidegger, such an 'anthropological' conception prevents us from appraising the true nature of our relationship with modern technology. It also leads us to think – wrongfully – that by simply improving and extending our technological tools, thereby enhancing our capability to "get things done", we will master technology itself and solve any problems that technology, as a system, may engender.

Papers I and V in this thesis illustrate that systematic attempts to refine technological devices and methods of application, such as *better visualisation of the fetus or development of a more valid cardiovascular disease risk scoring system*, do not necessarily eliminate the existence

[69] Reading Heidegger presents a major challenge, even to philosophers. I am not a philosopher, and this short passage is my first attempt to approach his teachings.

[70] Heidegger's thinking has contributed to such diverse fields as phenomenology (Merleau-Ponty), existentialism (e.g., Sartre), hermeneutics (Gadamer, Ricoeur), political theory (Arendt, Marcuse), psychology (Boss, Binswanger, Rolo May), theology (Bultmann, Rahner, Tillich), and postmodernism (Derrida). See The Internet Encyclopaedia of Philosophy. (www.iep.utm.edu/h/heidegge.htm).

of technology-related dilemmas. However, such refinements are likely to change the *nature* of the dilemmas.[71]

Heidegger attempted to capture the essence of technology with referral to the German word *Gestell* (English "enframing"). When technology is allowed to enframe our human drive for precise and scientific knowledge of the world, it also frames the nature of knowledge as such; i.e., *how* things can be known, and what there is reason to know. Thereby, everything considered real in the world becomes "material" which can be submitted to technological investigation and manipulation. From this perspective, the world is seen as *Bestand*, "a standing-reserve". Heidegger wrote – in his particular language style: "Modern science's way of representing pursues and entraps nature as a calculable coherence of forces." Man thereby 'summons' nature to fit into his plans. His view is that "technological enframing of the earth" is what constitutes *the essence of modern technology*.[72] In Heidegger's words: "The essence of modern technology starts man upon the way of that revealing through which the real everywhere, more or less distinctly, becomes standing-reserve." This involves "the destining into objectifying representation." Modernity is characterised by a relentless quest for certainty and for mastery, dating back to the days of the scientific revolution and Descartes (See Appendix 2). In such a framework, nothing is "good" in and of itself; it is good only if it is "good *for*" something. This moves us in the direction of a nihilism where all our options become increasingly technological and our values instrumental. And to a certain extent, Heidegger argued, modern technology is about to transform humanity itself into a standing-reserve.[73]

Heidegger did not focus on the question of whether technology is good

[71] To give an example of what this means, a British research team recently concluded that pregnant women in the UK have a history of being, and can still be, considered as "moral pioneers" in the face of steadily advancing prenatal screening technologies (Williams et al. 2005)

[72] Heidegger thereby sees reductionistic scientific theory as an aggressive, manipulative, and productive practice of control. *Thus, he collapses the distinction between theory and practice* (Milchman and Rosenberg 2003). Heidegger describes modern physics, a discipline originating in the 17th century, as the herald (messenger) of modern technological enframing. He, however, emphasises that the human *tendency for rational ordering and controlling of reality*, so strongly dominating the modern age, predated the development of the physical sciences. Physics should be regarded as a tool of technological control, not as the origin of modern technology as such. In other words, Heidegger believed that man's tendency for technological enframing of the world is part of our existential nature, present "prior" to modern physics.

[73] I suspect that Heidegger might have advised us to re-consider the use of the term "human resources" in relation to the staff in organisations, such as the hospital where I currently work.

or bad as such. And he was apparently not so much concerned with the world which technology may *reveal* as he was with the world it may *erase*. If technology's enframing of nature is unrestrictedly extended to humanity, we will suffer an existential "hollowing out," and that is a self-destructive course. Heidegger, however, saw both dangers and opportunities in relation to modern technology. "The essence of technology, as a destining of revealing, is the danger (...) But where danger is, grows the saving power also." It was Heidegger's advice that we accept the intellectual "gift of distress" (Deluca 2005) and reflect continuously and critically upon *enframing as the essence of technology*. If we do this, we are likely to acknowledge our responsibility towards humanity and the world we live in. Gracefully, he stated that

> For the saving power lets man see and enter into the highest dignity of his essence. This dignity lies in keeping watch over the unconcealment (...) of all coming to presence on this earth.

What people speak of as the 'problem' of technology therefore does not call for our abandoning it. According to Heidegger, the solution lies in constant and critical scrutiny of technology.

> Everything then depends on this; that we ponder this arising [of the saving power] and that, recollecting, we watch over it. How can this happen? Above all through our catching sight of what comes to presence in technology, instead of merely staring at the technological.

In Heidegger's own words, "Questioning builds a way."

2.4.3 Technology and values

The concept "*value*" is closely linked to technology. According to Merriam-Webster's dictionary (accessed 2005), value refers to "something (as a principle or quality) intrinsically valuable or desirable." The concept is difficult to define beyond that; it appears to have a variety of connotations, even within the field of ethics (Hofmann's thesis 2002:11). In this work, I will lean toward the definition Hofmann uses in his thesis, where he states: (2002:11) "*Value* refers to issues of the good life".

In the context of medicine, it can be argued that technology has become "the measure of all things" (Hofmann 2001:339), i.e., what is to be treated (or not) and how, and hence what is diseased and what is not. According to Hofmann, technology is essential to our understanding of

crucial challenges and dilemmas facing modern medicine, such as the discourses on medicalisation, somatisation, paternalism and autonomy. It is thereby reasonable to say that *whilst technology contributes to making medicine a scientific discipline, it also emphasises its moral nature.* US Professor of Philosophy H. Tristam Engelhardt Jr. describes modern medicine as "the most revolutionary of human technologies. (...) it restructures man and man's life. Medicine is not merely a science, not merely a technology, but it is the art of remaking man, not in the image of nature, but in his own image; medicine operates with an implicit idea of what man *should* be" (Engelhardt quoted in Zaner 2003:162). Medicine is thereby not merely *science in practice*, as most medical doctors may be used to thinking of it. Referring to the previous discourse on concealed powers, medicine can, from a certain angle, also be regarded as *normativity practiced in the name of value-neutral science* (this is a key element in Foucault's teachings; see also Canguilhem 1966; Jonas 1985).

2.4.4 Ways in which technology is value-laden

Heidegger warned against regarding technology as value-neutral. "We are delivered over to it [technology] in the worst possible way when we regard it as something neutral; for this conception of it, to which today we particularly like to do homage, makes us utterly blind to the essences of technology" (Heidegger 1977). Along the same lines, Bjørn Hofmann believes that technology should be seen as both *posing* and *promoting* issues of value. Two current medical topics may illustrate this double impact:

Technology promotes values. Technology is often purposefully developed on the basis of its desirable function. For instance, researchers have been trying to develop a device allowing insulin to be inhaled rather than injected.[74] This is motivated by the wish to make life more comfortable for people with diabetes mellitus.

Technology poses issues of value. Through a particular "action potential" of a general technology, it can come to pose new and particular value issues. One example is *fetal sex selection*. In the context of Western medicine, ultrasound technology has been developed for the purpose

[74] Rosenstock J et al. *Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes*. Ann Intern Med 2005;143:549-58.

of detecting structural fetal anomalies early in pregnancy. But once this has become possible, determination of the fetus's sex has also become possible. A new question of value thereby arises: "Is it morally defendable to use diagnostic ultrasound for the single purpose of identifying fetal sex?" (Jha et al. 2006).[75]

Technology is also value-laden in other respects. It strongly influences the *content and formation of medical knowledge*. What is seen as relevant and true in medicine is largely constituted by technology. Technology provides the basic entities and events that are applied in *defining diseases*, both in diagnostics and treatment, in clinical practice and research. It strongly influences the explanatory models of disease and medical taxonomy (diagnostic classification systems). The practical capability of technology may increase the sensitivity and lower the treatment threshold, resulting in increased occurrence of disease. Technology constitutes the signs, markers and end-points to be studied and manipulated (such as blood pressure, bone density, cerebral blood perfusion or clinical depression scales) in medical research. Technology thereby comes to direct how we as helpers act towards disease, and what we see as relevant therapeutical options.

Technology aims to eliminate the singularity of the patient and the subjectivity of the physician. It abstracts any given problem from the individual person in question (McWhinney 1989). Through technology, individual illness is translated into presumably objective data. This generalising attribute, which Hofmann refers to as "an *evaluative ignorance of the individual* in technological medicine" (Hofmann 2001:342), is however something which *emphasises* the value-ladenness of medical technology. This stands in contrast to the common claim that evaluating an individual by means of generalisations and abstractions is a value-neutral act.

[75] India's girl to boy ratio (aged 0-6 years) has declined from 945 to 1000 in 1991, to 927 to 1000 in 2001. In the most extreme geographical region, the reported ratio is 754 girls to 1000 boys. Explanations for these numbers include the traditional Indian penchant for a male son. The director of a leading non-governmental health organisation explains that pursuit of this culturally based value is made possible through the widespread availability and affordability of ultrasound machines. Despite legislation, sex determination tests have spread rapidly, even to remote areas. BMJ 2003;327:1007, doi:10.1136/bmj.327.7422.1007. A Lancet paper from 2006 addresses this issue in an empirical manner. It concludes that based on conservative assumptions, 10 million female fetuses are likely to have been selectively killed in India during the last 2 decades (Jha et al. 2006).

2.4.5 Who is in control – the doctor or the tool?

In his paper *Is there a technological imperative in health care?*, Hofmann investigates the argument that "technology has grown from being a tool to becoming a companion, and in some cases, the master of physicians" (Hofmann 2002:675). The relation between *technology*, on the one hand, and professional responsibility, on the other, thereby becomes a crucial issue to consider. Hofmann has investigated this question in a paper titled *Technological medicine and the autonomy of man* (2002), where he investigates to what extent a technological imperative in health care exists that can be seen as reducing our professional responsibility towards technology.

In the philosophical literature, one may find several different positions, referring to the way scholars perceive technology's value-ladenness and the degree to which we, as humans, can be regarded as in control of technology. The most clearly defined positions are:

i. Technology is value-laden – but we control it, by taking moral responsibility for the technology that we design, construct, produce, commercialize, promote, implement and use. Hofmann holds this position, and his paper on technology and autonomy of man ends with the statement (Hofmann 2001:166):

> Hence, technology is value-laden, but it is not imperative, and does not reduce our autonomy. This is particularly prominent in medicine, where issues of value are conspicuous.

In Hofmann's view, technology may however – for a wide range of reasons – appear *on the surface* to have an imperative character. He however argues that these *apparent* technological imperatives do in fact *emphasise and increase our responsibility in relation to its powerful potentials*. The conclusion of *Is there a technological imperative in health care?* (Hofmann 2002:687) is:

> It can be argued that there is no technological imperative in the sense that it reduces man's responsibility with regard to technology in health care. Human beings invent, construct, produce, commercialize, implement and apply technology, and as such are responsible for all these aspects of technology. (…) However, the individual healthcare professional and a specific healthcare institution can experience an imperative toward applying technology. Although such situations appear to reduce their responsibility, the responsibility is shifted, not diminished.

Many thinkers have however – in the spirit of Michel Foucault – emphasised that to the extent that humans control technology, the power to do so is not democratically distributed. It tends to be located with interest groups controlling both the general production of medical knowledge and the application of technology in the clinical setting. A key to understanding the development and spread of medical technology therefore lies in the study of societal power issues (see, for instance, Gillett 2004).

ii. Technology controls us (technological determinism). Many scholars have written about a "technological imperative" and demonstrated how technological values external to human values tend to enforce our actions in clinical practice (See, for instance, Tymstra 1989). Hofmann is concerned that referral to the imperative character of technology can be used as an excuse to disclaim responsibility. He refers to common phrases, such as "Progress can't be stopped," or "We have to use this opportunity, – or else someone else will."

In 1993, Eric J. Cassell published a seminal paper on the issue of technology and human control. It is titled *The sorcerer's broom. Medicine's rampant technology* (1993). Here, Cassell describes medical technology as having certain general self-perpetuating traits:

- Technologies originally come into being to serve the purposes of their users (i.e., medical goals direct technology), but ultimately their users redefine their own goals in terms of technology. Thereby, technological values come to foster medical values, which are values "intolerant of ambiguity". The human "quest for certainty"[76] drives the user to try to improve his or her technology. Technology thereby gradually comes to redirect the fundamental goals of health care. *In short, we gradually adapt medicine's goals to fit with technology's means.*
- *Technologies are reductive and oversimplifying.* Cassell sees technology's hold on medicine as the result of two prior reductive steps in the history of medicine: The *first* such step involved the reduction of the problem of human illness, with all its intricate physical, social, emotional and cultural aspects, to *the biological problem of disease*. The thus emerging precise definitions of dis-

[76] Note by LG: Physician Grant Gillett has also described this phenomenon, in a paper called *Clinical medicine and the quest for certainty* (2004).

> ease, in terms of anatomical, biochemical or otherwise measurable characteristics, are prerequisites for application of the scientific method of the natural sciences in medicine. The *second* reductive step follows from the scientific investigation of disease by use of technological investigation. Here, the findings from science come to represent the accepted picture of the disease. This closes the circle: *scientific knowledge that was gained by technology further promotes the application of technology.*

Cassell explains the rampant nature of medical technology with reference to human nature. "Technology is not the problem: it is the relationship to it of those who employ it that is problematic" (1993:32). This is captured by the metaphor *The Sorcerers broom* where the broom comes to live a life of its own in the hands of an apprentice who has not yet learned to master it.[77] Cassell perceives that what appears to us like a technological imperative is a result of human deficiencies: We have *a tendency to wonderment, an attraction for the immediate and unambiguous, a tendency to avoid uncertainty*, and an inherent *desire for power*. Cassell suggests that the solution to the problem of self-perpetuating technology is that we must learn to control ourselves, which means to learn to "tolerate uncertainty, accept ambiguity, deal with the complex, and turn away from mere wonder." In this way, Cassell strives to combine the notion of a technological imperative with the recognition that as humans, we are still responsible for how we use technology.

In 1999, James le Fanu stated that "the general, and probably correct, perception of medical technology is that it is out of control" (le Fanu 1999:252). In accordance with Cassell, he argues: "The culprit is not technology itself, but the intellectual and emotional immaturity of the medical profession which seemed unable to exert the necessary self-control over its new-found powers" (1999:261). A recent paper on the use of new medical technology in the USA illustrates that modern hi-tech medicine has indeed come to represent a profound, professional, everyday challenge to doctors, – here exemplified by the particular field of radiology:

[77] *The Sorcerer's Apprentice* is a poem by Goethe from 1779. In the sorcerer's absence the apprentice takes the sorcerer's magical broom, believing that he is in control of the device: "By my wishes now I've bound you." But then he realises that the spirits he has conjured come to live their own life, and they ignore him. The entire house is about to go under – and the apprentice has forgotten the word with which the master turns off the broom's magical powers.

> The cutting-edge technology of modern radiological imaging may capture the attention of patient and physicians alike, but it is incumbent on the physician to see beyond the enthusiasm and perform a rational analysis of the screening test in context. The Charter on Medical Professionalism espouses the view that physicians have a duty to 'create new knowledge and ensure its appropriate use' (Ashar et al. 2005).

2.4.6 Introduction of new medical technology – a history lesson by Ann Oakley

After studying the development and implementation of ultrasound in obstetrical care, UK professor of sociology Ann Oakley reflected upon lessons to be learned, to help us predict how things are likely to develop in other and future medical settings (Oakley 1986). Initially, she notes that "commercial interests are essential to consider when trying to understand the spread of a new technique, although it is extremely difficult to acquire reliable information on these interests" (Oakley 1986:6). She subsequently proceeds to outline what we can learn from the history of obstetric ultrasound:

1. Technical innovation in medicine is usually a serendipitous rather than a rational process. Thus, for example, the obstetric application of ultrasound developed somewhat incidentally (it began in Glasgow where ultrasound was much in use in the heavy steel industry).
2. Scientific evaluation of a new technique is not a necessary precondition for the introduction of that technique into routine practice. Ultrasound entered routine use in clinical practice before its effectiveness and possible hazards had been scientifically evaluated.
3. The time between experimental use of a new technique and its introduction into routine practice may be very short.
4. Because techniques like ultrasound form part of clinicians' professional resources, the experiences, opinions, and consent of pregnant women are rarely considered either necessary or valid in deciding on whom the technology should be used, or for what kind of indication.
5. As a final point, Oakley notes: "Advocates of a new technique are liable to suffer from a strange condition called certainty."

Paper I in this thesis outlines the development of fetal screening technology by way of ultrasound after 1986. It highlights that several of Ann Oakley's observations appear to have remained valid beyond the time period she herself investigated (Gabbay and Walley 2006).

3. THREE CLINICAL ARENAS STUDIED IN THIS THESIS

Three well-defined clinical arenas or 'scenarios' are analysed in Papers I-V in this thesis. These are:

1. antenatal screening and diagnosis by ultrasound, with emphasis on screening for chromosomal aberrations in the fetus,
2. the prevention of cardiovascular disease in clinical practice, and
3. the medical consultation in primary health care.

3.1 Antenatal screening and diagnosis by ultrasound

The setting for Paper I of this thesis, screening for fetal anomalies, is perhaps *the area in mainstream medicine where medical technology, social values and culturally determined meaning are most closely intertwined*. The moral value-ladenness of antenatal preventive/predictive medical technology (Solberg 2003) and the potential for unprecedented ethical dilemmas to arise as technology develops are, in my opinion, indisputable. On the 27th of October 2005, I received an e-mail from an experienced Norwegian general practitioner illustrating this. The GP knew that I had written about prenatal diagnosis and ethics and asked if I could send her my papers. Here is a quote from her letter (my own translation):

> Some years ago, there was considerable debate about prenatal diagnosis and ethical guidelines for its use here in Norway. To me, it looks as though this debate has disappeared; at least, I no longer know how the Norwegian healthcare system wants this problem / health service (?) to be handled. (...) As a GP, I am familiar with the criteria for referral to prenatal diagnosis. But then it is up to the hospital to decide on further procedures. (...) My concerns in relation to this matter increased this fall as a result of something I read in a newspaper: In a twin pregnancy, one fetus was diagnosed with Down's syndrome. It was aborted by injection of kalium into the fetus' heart so that it died.[78] It was somehow presumed that the other twin would be born quite prematurely, with the risks associated with that. Today, I read in another newspaper that a Danish doctor is facing a lawsuit because s/he had not discovered a fetus with Down's syndrome during screening. (...) Do you have a better overview of the development in this field than I do?

[78] This is called selective fetocide, a procedure used to kill one fetus selectively, see: Rustico MA et al. *Managing twins discordant for fetal anomaly*. Prenat Diagn 2005;25:766-71.

A brief account of the historical development as well as the current state of ultrasound screening for fetal anomalies (including referral to the above-mentioned lawsuit) can be found in Appendix 3.

Referring to Hofmann's conceptualisation of medical technology as the complex of *device, method and organisation* (Hofmann's thesis 2002:11), the technology analysed in Paper I can be described as follows:

device = ultrasound machine,
method = screening for fetal anatomy by ultrasound imaging,
organisation = antenatal care system.

In 2005, a UK research team addressed the relation between technology development and ethical dilemmas in a research paper titled *Women as moral pioneers? Experiences of first trimester antenatal screening* (Williams et al. 2005). The paper presents a qualitative study of the experiences of pregnant women undergoing first trimester ultrasound screening (synonyms: early ultrasound screening, nuchal translucency screening) in one of the most technologically innovative centres for antenatal care in the UK.

The study can be regarded as an empirical follow-up of the theoretical analysis contained within Paper I in this thesis.[79] The UK study opens with the words:

> The implementation of innovative medical technologies can raise unprecedented ethical, legal and social dilemmas,

and the conclusion is:

> …whatever other implications they may have, first trimester screening technologies continue the tradition of pregnant women acting as 'moral pioneers' in increasingly complex settings.

3.2 Prevention of cardiovascular disease

The clinical topic in Papers II, IV and V in this thesis is prevention of cardiovascular disease (CVD) in clinical practice. This is an interesting and important issue for at least two reasons. Firstly, CVD has been *the major cause of death and disability in the Western world* for several decades, due to what has been called "a modern epidemic of heart dis-

[79] The paper by Williams et al. (2005), opens and closes with reference to Getz and Kirkengen, 2003 (Paper I).

ease". This epidemic is said to have started in the 1930s, and reached its peak in the 1950s and 60s. Mortality from CVD has thereafter declined steadily (see figures 3.2.1. and 3.2.2). Secondly, *the tradition for individually oriented risk evaluation and modification* among asymptomatic individuals was first established in the field of CVD.

Appendix 4 contains a time-line of important and/or interesting (in the context of this thesis) events with relation to cardiovascular disease risk assessment and intervention. To mention a few items, the list begins with the invention of the sphygmomanometer and continues with the early, small-scale pioneering studies on hypertension control. Thereafter, the list highlights the huge and controversial studies on the relation between life style and heart disease in the 1970s and continues with the large-scale preventive drug intervention studies bearing catchy names, such as STOP, HOT, 4S, LIFE, PROSPER, etc. The time-line also highlights milestones in the development of medicine's theoretical understanding of the determinants and prevention of cardiovascular disease. The steadily decreasing cut-off points for definition of increased risk due to elevated blood pressure and cholesterol levels are noted, as are the correspondingly increasing sizes of the study population needed to ensure that the intervention studies have statistical power.

Paper II examines the particular task of implementing '*evidence-based medial knowledge' relating to one particular individual encountered in clinical practice*. Referring to Hofmann's definition, the technology being investigated can be conceptualised as follows:

device (or tool) = the narrowly circumscribed body of biomedical knowledge pertaining to this individual's situation, as defined by EBM,
method = implementation of EBM in clinical practice, and
organisation = primary healthcare system.

Papers IV and V deal with practical and ethical dilemmas related to implementation of the most recent (2003) European guidelines on CVD prevention in clinical practice (for further description, see the methods section). The technology being investigated is

device (or tool) = 2003 European guidelines on CVD prevention in clinical practice including the SCORE chart,

method = CVD risk assessment and intervention in routine clinical practice, and
organisation = primary healthcare system.

The following list gives a very brief outline of the work involved in cardiovascular disease risk assessment, intervention and monitoring of individuals persons/patients in primary health care:

- Determine the level of conventional CVD risk factors. Repeat initial measurements to avoid assigning the person to an incorrect risk group (misclassification).
- Estimate total risk for CVD. This involves combining conventional CVD risk factors (by use of the SCORE system).
- Intervene with the aim of reducing risk: offer life style advice and drug intervention, when appropriate.
- Control: monitor effects and reconsider therapeutic interventions, if necessary.
- Monitor potential side effects of therapy.
- Keep on inspiring the patient to make or maintain favourable changes, whilst keeping disease-related worries to a minimum.

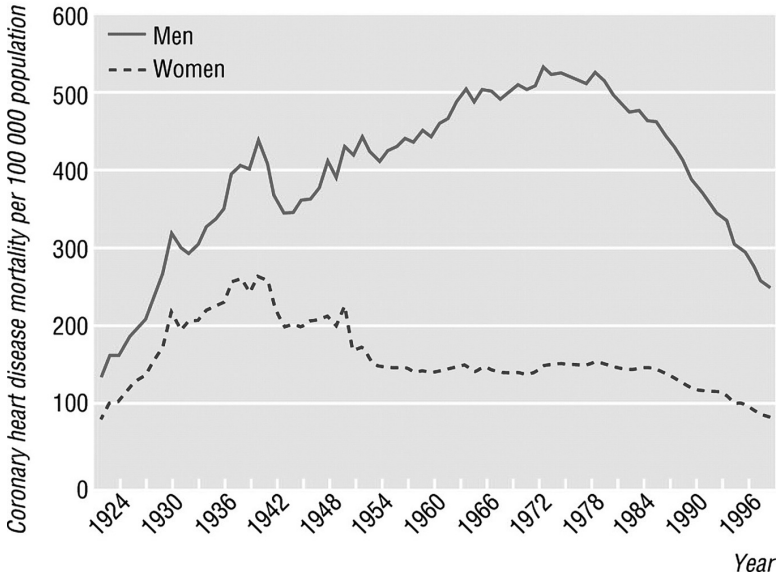

Figure 3.2.1 Secular trends in age-standardised mortality per 100 000 population for coronary heart disease for men and women 1921-98, England and Wales. Source: Lawlor DA et al. BMJ 2001;323:541-5.

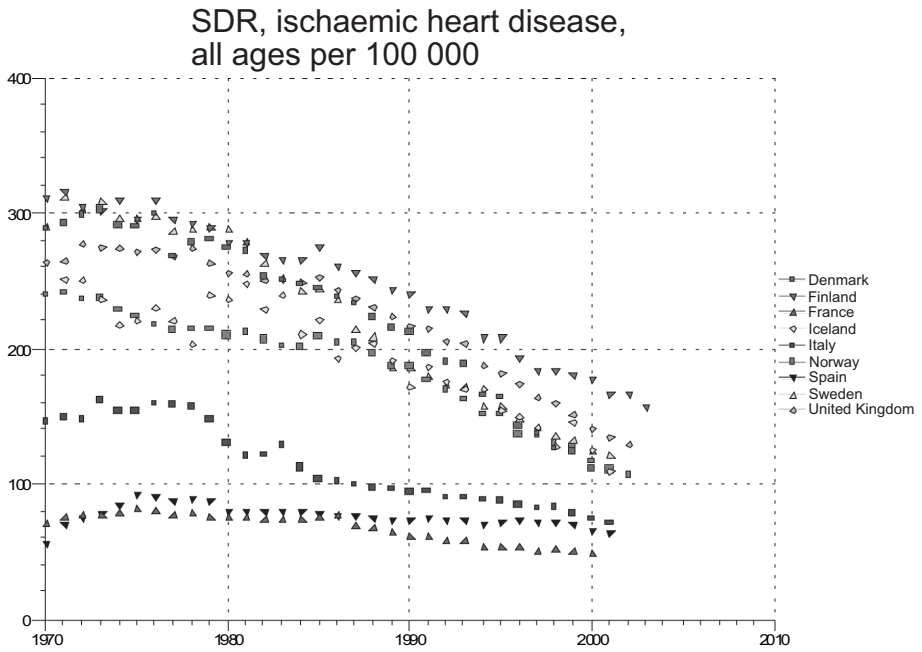

Figure 3.2.2 WHO statistics on mortality from ischemic heart disease in selected European countries 1970-2003. Source: the WHO's European Health for All database at www.hfadb.who.dk, accessed in February 2005.

3.3 The medical consultation in primary care

The consultation can be regarded as the heart of medicine. As I see it, *it is the clinical encounter which has legitimised the medical enterprise and given medicine its mandate from society from the times of Hippocrates*. In 1949, the English paediatrician Sir James Spence delivered a famous statement regarding this topic:[80]

> The real work of a doctor is not an affair of health centres, or public clinics, or operating theatres, or laboratories, or hospital beds. These techniques have their place in medicine. The essential unit of medical practice is the occasion when, in the intimacy of the consulting room or sick room, a person who is ill, or believes himself to be ill, seeks the advice of a doctor whom he trusts. This is the consultation, and all else in the practice of medicine derives from it.

[80] Spence, James: *The need for understanding the individual as a part of the training and functions of doctors and nurses.* [Speech delivered at a conference on mental health, held in March 1949]. In: The purpose and practice of medicine: selections from the writings of Sir James Spence. London: Oxford University Press; 1960, p 273-4.

Previously in this theoretical introduction, I have outlined how the medical 'preconception kit' (see chapter 2.2.4), which most practicing clinicians share, lays out the basic premises for what happens between doctor and patient in the consultation. Some of the historical premises for the biomedical approach to disease and suffering are outlined in Appendix 2. Sir James Spence wrote his speech, based on his experience as a practitioner of the full-blown, reductionist, medical paradigm (referring to the previously mentioned analysis by scholars, such as McWhinney, Leder and Cassell). Spence, however, practiced as a physician long before anyone had said that 'opportunistic health promotion' should be considered a self-evident part of the good consultation (the main topic of Paper III), very long before the times of 'evidence-based medicine' (a core topic of Papers II-V in this thesis) and, thereby, also long before authoritative clinical guidelines and clinical recommendations were developed in the preventive sphere (the topic of Papers II, IV and IV).

As mentioned in the previous section, the first milestone along the road towards the 'new' preventive paradigm was passed in relation to medical control of hypertension among asymptomatic subjects. James le Fanu (1999) has listed "the prevention of strokes by control of hypertension" (referring to a paper in The Lancet in 1964, see Appendix 4) as one of the 12 most important moments of 'the therapeutic medical revolution', which began around 1940:

> In the past people visited their doctors because they were ill or had some distressing symptoms about which they were concerned. Hypertension changed all of this (…) it expands the scope and influence of medicine enormously.

The clinical task of incorporating preventive medical activities into everyday clinical practice, whenever an opportunity to do so arose, gradually developed in the wake of this breakthrough. Such incorporation became formally acknowledged as a cornerstone of good practice in primary health care in general when Stott and Davis published their seminal 1979 paper *The exceptional potential in each primary care consultation*, where the concept 'opportunistic health promotion' was pinpointed. This paper represents the point of departure for the discussion in Paper III, which outlines the development since 1979 and examines to what extent Stott and Davis' consultation model fits with contemporary expectations and imperatives in the field of preventive medicine. The technology being investigated in this paper can thereby be described in terms of:

device (or tool) = preventive guidelines and recommendations,
method = opportunistic disease prevention, taking place in the context of routine consultations, and
organisation = primary healthcare system.

The technology being investigated in Paper II, which deals with the particular topic of the consultation in addition to the topic of cardiovascular disease, was outlined in chapter 3.2.

In this thesis, the doctor-patient relationship is addressed from the particular angle of opportunistic preventive medicine. This discussion may nevertheless be seen in light of more general developments apparently taking place in the doctor-patient relationship, if regarded from a general and more global perspective (See, for instance, a paper by Potter and McKinlay titled *From relationship to encounter: an examination of longitudinal and lateral dimensions in the doctor-patient relationship*, 2005).

4. AN ANALYTIC FRAMEWORK TO GUIDE FURTHER DISCUSSION

"The first decision to make when developing a public-health strategy must be to decide the philosophical basis on which it is to stand". This statement appeared in a *Lancet* commentary (McKee and Raine 2005) to the UK Department of Health's White paper *Choosing health: making healthy choices easier* (2004). Along the same lines, other public health researchers state that knowledge of philosophical theory is about to become equally relevant to the field of public health as knowledge about epidemiological methods (Roberts and Reich 2002). Personally, I am convinced that philosophical analysis is also relevant to the planning of *individually targeted preventive medical programmes*. One of the aims of this thesis is to present "*sustainable and responsible development*" as a conceptual framework for discussing the strategic and ethical challenges which are highlighted in the five sub-studies of this thesis (Getz et al. 2005).

As I see it, the idea of *sustainable and responsible development in preventive medicine* would have implications for

- medical theory building and development,
- medical research activities,
- medical practice organisation, integration and remote planning, and
- the individual clinical encounter.

In the following, I will briefly introduce the concepts *professional moral responsibility* and *sustainable development*. The introduction of responsibility will depart from the notion of medical *professionalism*.

4.1 On the moral responsibility of medical professionals

4.1.1 What does it mean to be a professional?

The first and paramount topic discussed in the 5th edition of the previously mentioned American College of Physicians' Ethics manual (see Snyder et al. 2005) is the notion of professionalism.

Medicine is "a profession to be entered," not only a trade to be learned. It involves "membership in a self-correcting moral community" (Snyder et al. 2005:576). "Being a professional is an ethical matter, entailing devotion to a way of life, in the service of others and of some higher good" (Kass 1983). UK Sociologist David Armstrong crystallises[81] the essence of a profession as a combination of:

- a *service ideal*, and
- an *esoteric knowledge base*.

The roots of medical professionalism date back to the teachings of Hippocrates (See Appendix 2). The word *profession* stems from the Latin professio, which means "public declaration." This indicates that professionals are expected to be *explicit and clear about their moral values* (Wynia et al. 1999). A *professional person* not only has particular knowledge and skills, acquired through regulated training and refined by experience but also conforms to certain standards of personal behaviour marked by honesty, ethical integrity, humility, compassion and empathy.

Quite a lot has been published in the medical literature on the topic of medical professionalism in recent years. In these texts, there appears to be consensus that the medical profession has a responsibility to protect not only vulnerable *persons* but also vulnerable *social values* (Wynia et al 1999, Rothman 2000).

Somewhat more specifically, a profession is characterised by (Snyder et al. 2005):

i. A specialised body of knowledge that its members must teach and expand. It is important to acknowledge that non-professionals cannot easily evaluate or regulate this body of knowledge (Irivine 1997).
ii. A code of ethics and a duty of service putting patient care above self-interest. By definition, a professional claims to be responsible – which means that s/he can be trusted to work conscientiously without supervision.
iii. A privilege of self-regulation granted by society. Competent self-regulation is a pre-requisite for professional independence (Irivine 1997).

[81] Lecture posted on the homepage of the Royal College of Physicians, see www.rcplondon.ac.uk. Accessed 2 Dec, 2005.

The literature indicates that self-regulation is not only a matter of keeping a watchful eye on the competence and abilities of individual practitioners of the profession. Essential features of professional self-regulation also appear to include (Irivine 1997 and 1999):

- ensuring that medical activity has well-defined purposes, values, and strategic direction that is compatible with public expectations.
- ensuring good and consistent performance, the use of set standards and quality-assurance.
- well-defined and well understood responsibilities and lines of accountability. Whenever possible, the process of regulation should be made visible and public.

In 2002, the US-European *Medical professionalism project* resulted in the publication of a *Physician Charter on medical professionalism*.[82] This charter lists a set of responsibilities pertaining to the medical profession. Among these responsibilities is a *commitment to scientific knowledge*. This commitment is further specified in the following way:

> Much of medicine's contract with society is based on the integrity and appropriate use of scientific knowledge and technology. Physicians have a duty to uphold scientific standards, to promote research, and to create new knowledge and ensure its appropriate use. The profession is responsible for the integrity of this knowledge, which is based on scientific evidence and physicians' experience.

I regard all five papers in this thesis as dealing with the challenge of maintaining the integrity and clinical relevance of the medical knowledge base in an era characterised by increasing biological reductionism, combined with ever stronger commercial influences (see, for instance, Moynihan et al. 2002; Lian 2003; Abramson 2004; Angell 2004; Nelkin and Andrews 1998).

For a long time, professionalism has been considered as a given in medicine, but with changes in the doctor-patient relationship and, more globally, in the way medical care is being delivered, the nature and role of medical professionals has come to be ever more often questioned and debated (Pereira Gray 2002). The contemporary analyses and critiques of medical professionalism can be exemplified by papers such as *The end of the golden age of doctoring* (McKinley and Marceau 2002). The

[82] *Medical professionalism in the new millennium: a physicians' charter.* Lancet 2002; 259:520-522 (The charter was also published in 29 other national and international medical journals).

debate is not new, however; the sociology literature has discussed and criticised the concept of professionalism since the 1970s.

It is difficult to arrive at a shared understanding of what ethically responsible, professional behaviour actually is, as long as the moral basis for our actions, i.e., the values on basis of which decisions are taken – is not reasonably clear and accepted by society as a whole. Until now many have considered the basis for responsible action in medicine to be connected with the Hippocratic Oath, but this code does not have any clear philosophical basis, other than that it was recognized by the inner circle of physicians. Modern dilemmas like the role of technology, public costs, the definition of life, genetic engineering and assisted suicide currently challenge the notion of moral integrity and responsibility in professionals in an unprecedented manner.

Some of the controversy regarding medical professionalism can be seen as stemming from different perspectives on what medicine is all about. Two quite polarised views of the nature of medicine and its goals can be said to exist, at least in the US context (Callahan 1996). One view discerns *inherent goals in medicine*, the other *external, socially constructed* goals. The 'inherentist' position has the doctor-patient relationship at its core and defines medicine's goals as healing, helping, caring and curing. The 'social construction position', in contrast, presumes that it is quite difficult to define a meaningful set of inherent values, and that medicine is best thought of as an evolving fund of knowledge and a changing range of clinical practices with no fixed essence – ready to respond to evolving societal expectations and demands.

In December 2005, an authoritative report on the topic of medical professionalism, authored by *The Lancet's* editor-in-chief Richard Horton, was released from a working group on behalf of the UK Royal College of Physicians (see Horton 2005). The report states that medical professionalism lies at the heart of being a good doctor, but that today's healthcare environment, which focuses on setting targets and regulation, puts this at risk. It states that "professionals and professional organisations are increasingly mistrusted." Richard Horton's conclusion, as he sums up the report in *The Lancet*, is: "Medical professionalism needs to be put back onto the political map of health" (Horton 2005).[83] The working

[83] The full report is accessible through www.rcplondon.ac.uk/pubs/books/docinsoc.

group proposes a new definition of professionalism, which the members believe to be more valid for our time: "*a set of values, behaviours and relationships that underpins the trust the public has in doctors*."[84] In other words, this definition focuses on partnership with patients and with other disciplines and disregards the classical focus on professional-clinical autonomy, privilege and self-regulation. The report also says that serious failures in leadership mean that the medical profession is currently underselling itself, due to a lack of a clear vision and coordination of activities: "While there are many leaders in medicine as a whole, there is little leadership in medicine as a whole. As a result doctors are too often seen as "negative, defensive and self-serving." It is also noted that "no single institution across medicine presently exists to define an overall vision for health from the profession. (…) We believe there is a case (…) to debate, explore, think about, study, and develop policies across the many different institutions of medicine." Finally, the working group perceives that "the regulatory pendulum" has swung too far in the direction of "rigorously enforced dutiful conduct [of doctors]." It believes that the pendulum "needs to be brought back to a more balanced position where there is an understanding that an environment which encourages a doctor's 'goodness' is one that will promote positive patient outcomes. This 'goodness' is what we mean by professionalism."

4.1.2 The reflective practitioner

In 1994-1996, I was member of a committee in The Norwegian Medical Association which planned continuous medical development in the field of general practice. In that setting, I was introduced to the works of professor of planning and education Donald A. Schön[85] (Schön 1983, 1987 and 1988). Schön's thoughts are in many ways relevant to this thesis. Based on research on the working lives and learning styles of professionals, he came to regard a *general ability to critically analyse and evaluate one's own experience and develop one's practice as a result* as a key characteristic (Schmidt 2000; MacLeod 2001). Thus, systematic engagement in reflective processes of 'design', i.e., processes of learning and inquiry, which aim to *change an existing situation into a pre-*

[84] It is specifically stated that in their day-to-day practice, doctors are committed to the following values, which form the basis for a moral contract between the medical profession and society: integrity, compassion, altruism, continuous improvement, excellence, and working in partnership with members of the wider healthcare system.

[85] Donald A. Schön (1930-1997) is regarded as one of the most influential thinkers in the theory of education and professional development in the 20th century.

ferred one, distinguishes professional practitioners. Organizations and individuals should be flexible and aim to incorporate lessons learned throughout their life, Schön called this 'organizational learning'. Schön argued that professional inquiry of this kind can be as rigorous as conventional research. In the methods section of this thesis (see chapter 7.1.3), I describe how clinical 'conversations with the situation' – a phrase borrowed from Schön – have been part of my reflective process as an academic.

4.1.3 "Once the rockets are up – who cares where they come down":[86] on the moral responsibility of scientists

As previously mentioned, Francis Bacon believed that knowledge contains the power to conquer what he perceived to be man's vulnerable and helpless natural condition. Since the times of the Scientific Revolution, the validity as well as the ethical implications of this statement have become increasingly clear. The ethical implications of man's search for knowledge relate both to what researchers *do* and do *not* invest themselves in. Related to researchers' negligence of important scientific topics, I would like to mention Yehuda Elkana (b. 1934), who is a scholar of the history, theory and politics of the sciences and Dean of the Central European University of Budapest.[87] Elkana believes that the majority of the contemporary academic world is currently very far from addressing the most central questions burdening humankind. Above all of these are poverty, mass-diseases like AIDS, ecological threats, and the future of democracy and human rights in the emerging global political systems.

If considering moral responsibilities related to what scientist *do* invest their resources in, it appears reasonable to reflect on the development in the field of nuclear physics. Until the Second World War, there was

[86] "*Once the rockets are up, who cares where they come down? / That's not my department, says Wernher von Braun*." This line comes from a Tom Lehrer song (1965) about the German scientist who led Nazi Germany's rocket programme before and during the Second World War, and who entered the United States at the end of the war through the then-secret Operation Paperclip. Von Braun became a naturalized US citizen, later joined NASA, and is regarded as a founding father of the United States space program. As Lehrer indicates, Von Braun has been characterised as the kind of researcher who is willing to serve any aims, provided the research is commissioned and funded.

[87] CEU is a US-style graduate university with a focus on the social sciences and the humanities. Elkana sees it as a major challenge to establish a global niche for creating new knowledge in areas where rethinking is necessary, and where rethinking is a question of intellectual risk-taking. Elkana claims that our traditional way of thinking in objectivities has to give way to thinking in complexities, since there is no single, valid method for understanding the human condition. See the university's homepage on www.ceu.hu/welcome.html.

a reigning conviction that by applying scientific methodology which secured the gathering of pure, objective and value-neutral knowledge, researchers did not bear any responsibility for the potential impact of knowledge application. This notion, however, started to change after the Second World War, both in the German[88] and the Allied setting. Some of the researchers contributing to the Manhattan project came to experience that their scientific contribution turned into a personal moral burden. An example of this was Albert Einstein, who in 1939 sent a letter to warn President Franklin D. Roosevelt that energy released in nuclear fission might be used in bombs by the Germans. After the bombing of Hiroshima, Einstein is said to have claimed: "I could burn my fingers that wrote that first letter to Roosevelt." Physicists had lost their scientific innocence, so to speak, and acknowledged that no clear demarcation line existed between *research*, on the one hand, and *application of the research*, on the other (Kirkengen: Rosendal lecture, 2005).

4.1.4. Heidegger on causality and responsibility

We are now in the post-war era where Martin Heidegger, in 1953, wrote *The Question Concerning Technology* (see 2.4.2). Contemplating the inherent dangers he saw in the way modern technology 'enframes' the world, Heidegger, in his poetical way, wrote:

> We look into the danger and see the growth of the saving power.

He continued by emphasising that *the essence of this saving power* lies in continuous and painstaking, critical reflection:

> Through this we are not yet saved. But we are thereupon summoned to hope in the growing light of the saving power. How can this happen? Here and now in little things, that we may foster the saving power in its increase. This includes holding always before our eyes the extreme danger.

As I see it, Heidegger is here calling forth the moral responsibility in every scientist and every professional, in our everyday work, for every project we engage in, world-wide. The word responsibility is derived from 'response' (in Latin, responsum means reply) and suggests that a

[88] A recent book demolishing the notion of scientific value-neutrality on the basis of the history of The Third Reich, is *Hitler's scientists* by John Cornwell at the Department of History and Philosophy of Science at Cambridge University (2003). Cornwell explores the general relationship between science and society and claims that it is naive to assume that in a democracy, this relationship may automatically be characterised as morally sound.

person who has responsibility must be prepared to respond to questions. The potential question awaiting a response may however be posed some time in the near or distant future. And the future will also reveal the possible questioner. It could, for instance, be a patient, a relative, society or a public body. It could also be yourself.[89] The question might apply to your personal decisions and actions, but it might also address actions in which you took part as member of a scientific group or a healthcare institution. In recognition of the latter, Dutch ethicist Martien Pijnenburg recently made a systematic attempt to outline how moral responsibility can be conceptualised as pertaining to healthcare organizations (Pijnenburg and Gordijn 2005). Pijnenberg's arguments build upon the theories of Canadian philosopher Charles Taylor, who was again inspired by Martin Heidegger.

Something particularly interesting in Heidegger's thoughts concerning technology, is how he connects two important – but, in our contemporary minds, quite separated – concepts; namely *causality* and *responsibility*. In Heidegger's view, the instrumental way of thinking which has become so prevalent in Western societies can best be captured by investigating our assumptions about causality. If we were able to understand modes of causality in the same way as the ancient Greeks did, we would come to consider causality in a broader sense than we do today, in terms of *ways of being responsible for things coming into existence*. We would see that our basic orientation towards the coming-into-existence, or the 'revealing' of the world, is linked to the outcome, and thereby has to do with responsibility.

Prior to the Roman introduction of the term causa, the Greek thought about causality in terms of *aition*. Aition meant "that to which something else is indebted." To encompass the meaning of aition, Heidegger used the German phrase: "das, was ein anderes *verschuldet*." The word verschuldet implies the same as aition; i.e., to be indebted, to owe, to be guilty, to be responsible for, and also to cause. According to the ancient Greek way of thinking about causality, causing something meant "starting something on its way to arrival." This means that *causality, moral responsibility* and *instrumentality* cannot be seen in isolation. Thereby, the one giving something a start, meaning one who "brings something into being", is respon-

[89] I came across this plain, but attractive, outline of what the notion of responsibility might mean to us as individual professionals in a paper called *Ethics in pharmacy: a new definition of responsibility* (Dessing RP, Flameling J. Pharmacy World and Science 2003;25:3-10).

sible for the bringing forth (Heidegger uses the term Hervorbringen), both in the sense of "that" and "how". This again means that technology (= how) is no neutral means to an end (= that). Technology is value-laden, it represents a particular way of revealing that which has been concealed. And the realm of revealing is the realm of truth.

4.1.5 Einstein: a man of conscience

In the post-war era, in parallel with Martin Heidegger, Albert Einstein came to focus ever more strongly on the fundamental moral challenges which modern science and technology are facing. This gradually led to the *Russell-Einstein Manifesto* in 1955 and establishment of the Pugwash Movement in 1957.[90] In 2005, an editorial in Scientific American was devoted to Einstein's sense of social responsibility as a researcher. In memory of the formula $E = m{\cdot}c^2$, it was titled: Einstein = Man of Conscience^2 and ended with the words:[91]

> Today, when prominent researchers comment on environmental politics, missile defence, health care priorities and similar matters, critics sometimes suggest that science and politics should not mix. But Einstein knew that scientists have a moral responsibility to explain their work, including its political implications. To argue otherwise is to say that science does not matter.

Interest in discussing scientific responsibility currently appears to be on the rise, even in peaceful democratic countries. In Berlin in 2005, a conference called *Einstein weiterdenken* (Thinking with Einstein, www.einstein-weiterdenken.de) was held, as "an invitation to re-examine the ethical and political responsibility of science in a globalised world." In Norway, a recent issue of the journal *Forskningsetikk* (*Research ethics*, the newsletter of the national research ethics committees in Norway)[92] was dedicated to the topic of scientific responsibility. To illustrate how discussions about the moral responsibility of medical researchers may look in our contemporary hi-tech research environment, we may look once again to the previously mentioned field of neuroscience. In a 2004

[90] In 1995, the Nobel Peace Prize was awarded in two equal parts, to Joseph Rotblat and the Pugwash Conferences in Science and World Affairs. The Pugwash Conferences were based on nuclear scientists' recognition of their responsibility for their inventions. Pugwash was the name of the location of the first meeting (Pugwash, Nova Scotia, 1957). The stimulus for that gathering was the manifesto issued in 1955 by Bertrand Russell and Albert Einstein, accompanied by other renowned scientists of the time. The manifesto called upon scientists to assemble to discuss the threat posed by the advent of thermonuclear weapons. The closing paragraph contains the sentence "Remember your humanity, and forget the rest" (See www.pugwash.org).

[91] Editors. *Einstein = Man of Conscience*^{2}, September issue 2004. See www.sciam.com, (accessed Sept 16, 2005).

[92] Forskningsetikk No 2, 2005.

lecture[93] at the US Society for Neuroscience, Researcher Stephan L. Chorover at the Massachusetts Institute of Technology claimed that the most important ethical questions in contemporary neuroscience are not the narrow questions which are currently posed by neuroethicists, which address the technical details of exactly how to perform research which involves brain surveillance and manipulation of the human brain in an ethically correct manner. Chorover perceives that the most essential questions to be asked in relation to this field are far more fundamental; they relate to *whether* the research should be done at all:

> Is applied neuroscience helping to enhance the quality of human life? Is it promoting sociotechnical dehumanization? What might be done to give neuroscience and neuroscientists a better chance of contributing responsibly to the emergence of a more just, participatory, and sustainable society?

4.1.6 Hans Jonas on medicine, technology and responsibility

The Western philosopher best-known for reflection on medicine, technology and moral responsibility is German-English-American philosopher Hans Jonas (1903-1993).[94] As previously said, Jonas was a student of Heidegger. He believed that taking moral responsibility is an essential part of being human, something "instituted by nature" (Bernstein 1995). In 1979, he formulated this as "the principle of responsibility" in a book titled *Das Prinzip Verantwortung. Versuch einer Ethik für die technologische Zivilisation* (English translation 1984, see reference list). Jonas believed that knowledge 'production' in general, and knowledge production related to human life and the human body in particular, imply a major moral challenge.

With time, Jonas became ever more interested in the relationship between technology and medicine. Scientists and clinicians, thought Jonas, must take great care to preserve *the wholeness and integrity of life* as they work to develop and implement new medical technologies. The following passage from his 1985 book *Technik, Medizin und Ethik*,[95] encapsulates Jonas' thoughts:

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[93] Chorover SL. Whither neuroethics? A developmental perspective. Lecture given in the Society for Neuroscience, San Diego, Oct. 25th 2004.

[94] For more about Jonas, see for instance Hans Jonas-Zentrum Berlin at www.hans-jonas-zentrum.de. A fine book about Hans Jonas in Norwegian is: Fidjestöl A. *Hans Jonas*. Oslo: Universitetsforlaget, 2004.

[95] This book – as far as I know – has not been translated to English. Translation from German by Anna Luise Kirkengen.

> It is argued that natural scientists are not responsible for what others do with the results of their research. If research were just contemplation, pure thought so to speak, this position, though still problematic, could eventually be defended. However, basic research is already to a considerable degree in itself also an action. This is expressed in the technology implied and the prior societal investment into the construction of these technical devices. Action is always already part of modern research. It is no longer like how Aristotle perceived nature, or how Copernicus and Keppler observed the universe and the stars without being able to interfere. Nowadays, every act of acknowledging and penetrating the secrets of nature already represents a manipulation of nature. We are aware that knowledge results in capability; capability leads to acting, and this acting turns into imperative action, that we must do what we can do. In case we can foresee that certain consequences of this chain of cause and effect may lead to a disaster, the question arises where to interrupt the process – or whether one should do so already at the source of knowledge, on the level of basic research. The latter would provoke most opposition (1985:304).

I will close this chapter on professional responsibility in medicine with a final quote from Hans Jonas (1984). It relates to his "imperative of responsibility," and builds a bridge to the next, and final, theoretical concept I will introduce, which is that of 'sustainable development':

> In your present choice, include the future wholeness of Man among the objects of your will.[96]

4.2 The concept of sustainable development

4.2.1 Historical background and definition

The word 'sustainable' comes from Latin *sustere*, which means to uphold. The use of the word has developed over time. It originally referred to harvesting of single resources; subsequently it was used in relation to more complex ecosystems, and more recently it has come to encompass the integrated social-physical-economical welfare of communities (Lafferty and Langhelle 1999). The concept 'sustainable development' first appeared around 1980.[97] As mentioned in the opening of the thesis, it was brought to world-wide attention in 1987 in the report *Our Common Future* (1987). *Our common future* gave the concept of sustainable development unprecedented political authority as a theoretical framework for discussing issues related to growth and development.

[96] "Handle so, daß die Wirkungen deiner Handlungen verträglich sind mit der Permanenz echten menschlichen Lebens auf Erden."

[97] The 1972 book *The limits to growth*, published by the interdisciplinary group "Club of Rome" (Meadows D. et al.) is considered among the important works preceding the discourse of sustainable development.

Sustainable development is a complex and contested concept (Jacobs 1999). However, there is agreement that it *embraces the notions of 'needs' and 'limits' and describes a process of transformation where resource use, investment, technologies, institutions and consumption patterns do not occur at the expense of environmental degradation*. Sustainable development can be regarded both from a local and a global perspective. Various formal definitions of the concept have been proposed, but the best-known is still 'the Brundtland definition':

> Sustainable development is meeting the needs of the present generation without compromising the ability for future generations to meet their needs.

The Brundtland Report addressed environmental and socio-economic sustainability from a relatively pragmatic viewpoint. It regarded economic growth as something basically 'good' and encouraged development of currently impoverished regions of the world whilst aiming to maintain a high living standard in affluent countries. The view of sustainability presented in the report has thereby been widely criticised as too "weak." It has also been accused of being too "fluid," because *Our common future* does not go very far in making the vision "technically operationalisable." Many scholars however believe that the universal appeal and political potentials of the concept 'sustainable development' are dependent on the fact that the concept appears relatively neutral and flexible (Jacobs 1999). Their argument is that although the Brundtland Report is not very radical as such, the discourse on sustainable development can open *new windows of opportunities* where it becomes possible to pose critical questions and draw attention to previously unacknowledged, down-prioritised and sensitive issues on the political or societal agenda.

It must be noted that *sustainability* – defined as the quantitative capacity to uphold some phenomenon or activity – contains no statement about the moral value of the activity as such. The discourse on sustainable *development* thereby presupposes a wider ethical framework defining certain values that are linked to human and societal well-being and prosperity (Dower 1997).[98] As Canadian philosopher Ingrid Leman Stefanovic has pointed out, "in this technological age, sustainability clearly

[98] An anthology reflecting the Norwegian discourse on sustainable development has been written by Lafferty and Langhelle (1999).

becomes more than a technical issue. It is also, in fact, a philosophical matter" (Stefanovic 2000). And this is where the moral notion of *responsibility* comes in.

As previously mentioned, the medical community has so far contributed very little to the debate on sustainable development. Daniel Callahan is in fact the only writer I have come across who has systematically attempted to investigate what sustainability might mean in a medical context. (See the report from *The Goals of Medicine Project* edited by Callahan in 1996 and Callahan's book *False hopes* from 1999.) Callahan is a *communitarian* thinker focusing on what one may call social ethics, "the common good" and public interest, as opposed to an ethics focusing on the individual. Callahan believes that ethical analysis must take the social implications of medical activity seriously and not simply assume that medicine can be directed by autonomous choices made by isolated individuals. Relations between a public healthcare system, technological advancements and the health problems of individuals are very complex. Every professional proposal, decision or intervention has private as well as public aspects (Callahan 2003). As he addresses the topic of sustainability, however, Callahan examines medicine in general, as it is currently evolving in the USA, where the world's highest economic expenditure on health exists together with dramatic inequalities in access to services. It is important to note that the present thesis relates to preventive medicine in the context of the far more egalitarian Nordic welfare systems where healthcare has been regarded as part of the primary benefits of society, along with rights to education and political rights. Despite these contextual differences, it nevertheless appears relevant to sum up what Callahan believes to be the essence of sustainable medicine (Callahan 1999 and 2000):

- First: from an economic perspective, *no* society can any longer afford to maintain unlimited progress as its ideal.
- Second: there are better ways to promote health than surrendering to a strong dependency on technological medicine.
- Third: all of us will do better in terms of health, provided we conceptualize it within categories of the common well-being of whole populations instead of only chasing individual benefit/advantage.

4.2.2 General prerequisites for sustainable development

The prerequisites for sustainable development have been examined

from a variety of angles in recent years. Several scholars appear to agree that it is possible to outline a set of 'intermediary principles', something between abstract ideals and technically operationisable reality (Lafferty and Langhelle 1999). As such, these principles are comparable to the previously discussed principles in medical ethics. The following list contains the principles I have most frequently come across in texts on sustainable development. My main reference in this field is a paper written by Michael Jacobs, titled *Sustainable development as a contested concept* (Jacobs 1999).

1. Policy integration. This implies ensuring that economic development and environmental protection are integrated in planning and implementation. Fragmentation of responsibility can generally be seen as a major obstacle to sustainable development. It is important to challenge compartmentalised groups of decision-makers, for example, medical expert communities, to broaden their horizons. This may call for creation of new administrative structures, reform of existing institutions, and transformation of established policy-making processes.
2. Participation and democracy. This involves recognising that sustainable development requires the political involvement of all stakeholder groups in society.
3. Equity. This emphasises a commitment to meeting at least the basic needs of those having the greatest need, depending on the context (global/national/local perspective). One is also called upon to consider equity from the perspective of future generations' needs.
4. The precautionary principle related to environmental protection. This implies a systematic commitment to anticipating and reducing the risk of detrimental effects (such as pollution) and environmental degradation as a result of current activities. The sustainable development paradigm emphasises that complexity and uncertainty surrounds decision-making, particularly in situations where complex technical and scientific issues are involved. This highlights the relevance of what has been designated "the precautionary principle." This principle states that lack of scientific certainty should not be used as a reason for postponing measures to foresee and prevent potential detrimental side-effects of current or planned activities.
5. Planning for the future. Sustainable development is something

that must be carefully planned. There are too many complex interdependencies between political, social and economic factors to leave development to chance.

6. One final element appears on Michael Jacobs list which is not found in all overviews of sustainable development. This is the notion quality of life.[99] As I understand Jacobs, this concept aims to highlight that *growth* (which can potentially be sustained in a technical sense), is not necessarily equivalent to valuable *development*[100] that is good for human beings or the earth in the long run.[101]

In the discussion chapter, I will depart from the notion of 'sustainable and responsible development' and examine what this might imply in the context of preventive medicine.

4.3 Man as 'standing-reserve'?

I will close this theoretical introductory part with some personal reflections and questions anchored in Heidegger's and Foucault's writings on technology. As previously outlined, these philosophers were very influential. My acquaintance, however, with Heidegger and also partially with Foucault took place when I wrote the final papers in this thesis. Nevertheless, once I entered their thought universes, I realised that all the papers can be seen as representing examples of the kind of technological questioning and critique which these two thinkers called for. The conceptual frameworks presented by Heidegger and Foucault have facilitated my attempts to understand more deeply why and how implementation of new scientific knowledge in everyday practice can lead to the emergence of new and unacknowledged ethical dilemmas.

At first glance, the writings of Heidegger and Foucault appear very different. However, as others have documented (see Milkman and Rosenberg 2003), their teachings can be seen as closely connected. Heidegger probably did not know Foucault, but Foucault read Heidegger's works.

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[99] This should not be confused with the phrase 'quality of life' as it is frequently used in the context of medical research.

[100] In the introduction to this thesis, I presented the JAMA paper by Fisher and Welch (1999), which addresses the difference between growth and development in the medical context.

[101] In a general discussion of sustainable development, this perspective may be extended from the human society to life on earth in general, but in the context of this thesis, I will stay within the realm of human medicine.

In fact, Foucault maintained that his entire philosophical development was determined by Heidegger, although he very rarely quoted him directly (Milchman and Rosenberg 2003). The two philosophers worked very differently and addressed technology from very different perspectives. Heidegger's thinking can be characterised as meditative, and he focused on *the domination of nature by the natural sciences in a rather abstract manner*. The documents he investigated were classical texts in the history of Western metaphysics, with an emphasis on ancient Greek thought prior to 'technologization' as we know it today. In contrast, Foucault wrote in a rebellious manner about *the recent history of human sciences and the institutions in which they are embedded*. His research builds on the practical documents of everyday human life, such as administrative treatises, architectural plans, case studies and hospital records. But if we look beyond these fundamental differences, both Heidegger and Foucault critically scrutinised the same topic; i.e., how a reductionist, Cartesian world-view[102] has come to dominate human sciences and institutional practices. Both thinkers can be envisioned as engaged in *freeing the concepts of scientific 'knowledge' and 'truth' from what they perceive to be repressive epistemological constraints*. They warned against what Heidegger called "forgottenness of being" (*Seinsvergessenheit*).

Both Heidegger and Foucault have been accused of technological nihilism. These charges can however be refuted. Although they were both occupied with the destructive potential of technologies, none of them should be classified as technological determinists or as opposed to technology in general (see Sawicki's essay in Milchman and Rosenberg 2003).

I will now formulate three questions related to the way medical technology can be seen as conceptualising man, from the point of view of man as a standing-reserve:

First, Heidegger reminds us that *technically correct facts* may be far from what the old Greeks would have called *the truth*. He says:

> In a similar way the unconcealment in accordance with which nature presents itself as a calculable complex of the effects of forces *can indeed permit correct determi-*

[102] A brief account of the Scientific Revolution and René Descartes' thoughts can be found in Appendix 2 of this thesis.

> *nations;* but precisely through these successes *the danger can remain that in the midst of all that is correct the true will withdraw* (Heidegger 1977:26-7, italics by LG).

Correspondingly, and in relation to the particular context of medicine, Foucault observed how what he called disciplinary technologies of power/knowledge are far from neutral. They systematically "push" medical inquiry in the direction of isolating abnormalities requiring even further inquiry. He speaks of "laboratories of power... [in which] knowledge follows the advances of power, discovering new objects of knowledge over all the surfaces on which power is exercised" (Milchman and Rosenberg 2003:63). It thereby becomes quite apparent that Foucault's technologies of power can be expected to function quite anonymously in everyday life in much the same way as Heidegger's account of technological enframing. We are typically talking about everyday technologies that can be seen as implemented by no one and everyone, and quite typically in the name of goodness and progress.

As a medical doctor with an academic interest in preventive medicine and associated technologies, I pose the following question to reflect Heidegger's and Foucault's concerns:

Can it be that professionals as well as lay people are currently becoming increasingly distracted and desensitized, as a result of medical technology's particular way of enframing the human condition, in such a way that we lose sight of the essence of what it means to be human, in sickness and in health?

More concretely, the following question appears to become increasingly relevant in the preventive setting: *How can I, as a professional, be confident that my (supposedly) systematic and technically correct measurements of certain biological variables, such as cholesterol, or homocysteine, will result in a representation which is so true that it warrants the status of "that which matters the most" in relation to the health of the particular person in question?*

Second, Heidegger warns us that technological 'enframing' implies a danger that man becomes alienated from himself in an existential sense. By treating others as though their essence can be understood and calcu-

lated according to the laws of nature (a standing-reserve), we are about to reduce ourselves as human beings and lose sight of who we are. Heidegger says (1977:27-8):

> As soon as what is unconcealed no longer concerns man even as object but does so, rather, exclusively as standing-reserve, and man in the midst of objectlessness is nothing but the orderer of the standing reserve, then he comes to the very brink of a precipitous fall; that is, he comes to the point where he himself will have to be taken as a standing-reserve. (...) *Enframing endangers man in his relationship to himself and to everything that is* (...) *it drives out every other possibility of revealing* (...) The rule of Enframing threatens man with the possibility that it could be denied to him to enter into more original revealing and hence to experience the call of a more primal truth.

As a medical doctor currently working as the staff physician of a busy university hospital with a 'culture' that moves steadily towards the crossroads where "biologism" meets "economism"[103] (key-words: subspecialisation, financing by diagnosis-related-groups, a vocabulary related to production and customers, and leadership strategies derived from "human resources management" theories), I allow myself to pose a question which can be found between the lines of all the papers of this thesis, and which will be briefly addressed in the discussion of this thesis:

Could it be that the increasing international focus on dissatisfaction and 'burn-out' among healthcare personnel in general and doctors in particular[104] is related to and may even represent an early warning sign that the combination of modern *medical* and *management technologies* implies an unprecedented potential to alienate the professional helper from a genuine experience and understanding of what it means to be a human being who cares for other human beings?

Third and finally, let us revert to the ancient Greek way of "knowing how to bring forth" (reveal), also called *techn*E. TechnE involved an

[103] I owe the phrase "biologism meets economism" to previous CEO of the Karolinska Hospital in Stockholm May-Len Sundin, who is concerned about these matters and has shared her thoughts with me on several occasions.

[104] See, for instance, the theme issue of British Medical Journal on April 6th 2002, titled *Unhappy doctors* and the paper *Why are doctors so unhappy?* by Richard Smith (BMJ 2001; 322: 1073-4) along with the electronic responses which followed on bmj.com. I will not go further here into the literature on doctors' health and well-being in this thesis.

act of creation, of *poiesis*. Modern technology, too, is in a sense revealing. However, according to Heidegger, revealing by modern technology does not unfold into a bringing-forth in the sense of poiesis, but rather in a *challenging* (Herausfordern) manner. The German term Herausfordern has particular connotations relevant to an understanding of the difference. "Zu fordern" means "to demand, to summon, to crave." Here is the source for the difference of impact modern technology takes on what it reveals: it exercises *a new form of revealing that is not 'poetic', it is challenging and ordering* in an almost aggressive sense. It objectifies and subordinates that which it reveals. And that which is objectified is simultaneously subjected to be "Bestand", a standing-reserve, something "on call for use."

Introduced into the realm of medicine, the Heideggerian way of interpreting technology raises fundamental questions related to the human body as a potential resource to be manipulated commercially for scientific and therapeutic purposes, as well as for the purpose of profit (Nelkin and Andrews 1998):

In a context where human beings are 'known' to medicine by technological measures only, we accept that man is being included in Heidegger's standing-reserve. But, if everything is to be known as objectified only, where do we draw the limits for manipulation? How can we then protect ourselves and our patients from medico-technological exploitation and colonisation of all aspects of our being human? If man becomes a standing-reserve, what happens to human dignity in the medical context?

5. LIST OF PAPERS

I. Getz L, Kirkengen AL. Ultrasound screening of pregnancy: Advancing technology, soft markers for fetal chromosomal aberrations and unacknowledged ethical dilemmas. *Social Science & Medicine* 2003; 56:2045-57.

II. Getz L, Nilsson P, Hetlevik I. A matter of heart. The GP consultation in an evidence-based world. *Scandinavian Journal of Primary Health Care* 2003; 21:3-9.

III. Getz L, Sigurdsson JA, Hetlevik I. Is opportunistic disease prevention in the consultation ethically justifiable? *British Medical Journal* 2003;327:498-500.

IV. Getz L, Kirkengen AL, Hetlevik I, Romundstad S, Sigurdsson JA. Ethical dilemmas arising from implementation of the European guidelines on cardiovascular disease prevention in clinical practice: descriptive, epidemiological study. *Scandinavian Journal of Primary Health Care* 2004;22:202-8.

V. Getz L, Sigurdsson JA, Hetlevik I, Kirkengen AL, Romundstad S, Holmen J. Estimating the high risk group for cardiovascular disease in the Norwegian HUNT 2 population according to the 2003 European guidelines: modelling study. *British Medical Journal* 2005;331:551-4.

6. AIMS OF THE STUDY

The paramount objective of this project is to contribute to critical reflection and theory development in medicine by performing a systematic documentation, analysis and conceptualisation of possible, unacknowledged ethical dilemmas arising from clinical implementation of advancing, preventive, individually targeted medical technology.

Five different papers have been written to address this problem from different clinical angles, with the aims to:

1. Document and analyse the relation between advancing ultrasound imaging technology, the identification of soft markers for fetal chromosomal aberrations (most often Down syndrome) in the unborn child, and the rise of novel ethical dilemmas, with reference to the period 1980-2000.

2. Document and explore inherent difficulties and dilemmas related to implementation of so-called *evidence-based medicine* (EBM) in relation to individual persons/patients.

3. Conceptualise and discuss the aggregated implications of advancing preventive technology in the form of authoritative clinical guidelines and checklists in the context of everyday clinical practice in primary health care.

4. Model and reflect upon the consequences of implementing the *2003 European guidelines on cardiovascular disease prevention in clinical practice* in an unselected Norwegian population;
i. In a study including an empirical analysis and subsequent discussion of the proportion of individuals who exhibit unfavourable levels of the single cardiovascular disease risk factor of blood pressure and/or cholesterol, as defined by the guidelines cut-off points.
ii. In another modelling study discussing the prevalence of individuals becoming classified as 'at high combined risk' for CVD and in need of maximal clinical attention, as defined by the guidelines' SCORE system.

Finally, it is an aim of this thesis to present the idea of "*sustainable and responsible development*" as a conceptual framework for addressing the ethical and practical challenges that are highlighted by the five sub-studies of this thesis. This will be attempted in the discussion part of this thesis.

7. MATERIAL AND METHODS

The question being asked determines the appropriate research architecture, strategy, and tactics to be used – not tradition, authority, experts, paradigms, or schools of thought. *– Sackett & Wennberg 1997*

The present work builds on two distinctly different scientific approaches:

1. Conventional empirical analysis of population data. Papers IV and V build upon *empirical analyses of selected cardiovascular disease risk factors throughout a well-defined Norwegian population*. These analyses were undertaken in the wake of a pilot study (see chapter 7.2.4), which indicated that our concerns were justified, to demonstrate the existence of unacknowledged ethical dilemmas in relation to preventive medicine. The epidemiological analyses indicate the need for systematic and critical reflection upon the theoretical foundations for, and philosophical aims of, individually targeted initiatives in clinical practice.

2. Systematic, critical appraisal of existing medical evidence and clinical recommendations with regard to inconsistencies implicit in their frame of references. In papers I, II and III, the data material submitted to further analysis consists of *previously published scientific medical knowledge and clinical recommendations*. In other words, it is the theoretical foundation for recommended medical practice that is being investigated. Such a critical appraisal of valid knowledge on the level of epistemology is commonplace and considered appropriate in many academic disciplines, such as in the theory and history of science and in the political and social sciences. It is, however, not common in medicine to conduct studies to address, identify and evaluate the theoretical sources of problematic aspects of medical knowledge or practice. Consequently, such an approach is neither well established nor standardized in the context of traditional medical knowledge production. Both research approaches, however, must be considered equally necessary and appropriate to assure both theoretical consistency and methodological adequacy with regard to the conduct of research. Also, both approaches are equally and explicitly in accordance with *Encyclopaedia Britannica's* definition[105] of *research*, which is

[105] *Encyclopaedia Britannica's* on-line dictionary (Merriam-Webster), accessed Sept 7, 2005.

> studious inquiry or examination; especially: Investigation or experimentation aimed at the discovery and interpretation of facts, revision of accepted theories or laws in the light of new facts, or practical application of such new or revised theories or laws.

Later in this chapter, particular methodological issues pertaining to the different papers will be presented. I will however begin by outlining what I regard as fundamental premises for the reflective process leading up to this thesis.

7.1 Outline of the premises of my research process

7.1.1 Exploration of the scientific literature

From the mid 1990s, I have been exploring peer-reviewed medical literature, selected papers from other academic disciplines, as well as textbooks in the fields of philosophy, ethics, medical history, anthropology and sociology. Since I started this process, it has become increasingly easy to access full-text articles directly via the Internet. Not having to formally prioritise, finance, order and wait for papers has made roaming around in academic cyberspace ever more rewarding.

My search for literature has been driven by a combination of 'systematic rationality', where I have searched for documentation related to relatively sharply defined questions, and 'intuition,'[106] where I have pursued information or ideas that have attracted my interest, although the implicit relevance of this material did not always become explicitly clear to me until later. In the process of writing up this thesis, however, I have found that most of my topics of interests have come to fit together in a coherent fashion. They now constitute the foundation of the introductory theory chapter and the discussion of this thesis, and they can all be linked to the notion of 'sustainable and responsible medicine'.

The references constituting the empirical and theoretical basis and the discussion of this thesis cover a wide spectrum. Besides various psychological, sociological, philosophical, anthropological and historical papers and books, this spectrum encompasses

[106] Trisha Greenhalgh, professor of general practice with much experience in the fields of both evidence-based medicine and narrative-based medicine, defines professional intuition as "a decision-making method that is used unconsciously by experienced practitioners but is inaccessible to the novice. It is rapid, subtle, contextual, and does not follow simple, cause-and-effect logic. (…) Intuition is not unscientific. It is a highly creative process, fundamental to hypothesis generation in science" (Greenhalgh 2002).

- traditional epidemiological and clinical research,
- studies on the benefits and harmful effects of screening programmes,
- studies on risk assessment and communication,
- discussions of the development and implementation of clinical guidelines,
- discussions on medicalisation,
- basic research within the fields of psycho-neuro-immunology and fetal development,
- studies on the relation between social inequality and health,
- studies of the doctor-patient relationship and medical professionalism,
- critical analyses of contemporary biomedical and bioethical reasoning, and
- studies on the health and well-being of healthcare professionals.

7.1.2 Arenas for critical reflection and 'respectful dialogue'

In 2000, I found a paper in *The Lancet* which fascinated and stimulated me. Its title was *The idea is more important than the experiment*, authored by UK professor of cardiology John Martin. There, Martin presents an outline of academic processes that he thinks are likely to foster development and innovation in medicine (Martin 2000). He emphasises three things, which I have, through my own experience, come to understand and appreciate more and more:

> Scientific concepts are put together often most fruitfully in a non-linear fantasy, which is both spontaneous and intuitive.
>
> A multidisciplinary team is more likely to give rise to non-linear fantasy than a monovalent team.
>
> Perhaps the great problem of the next 100 years (...) will be to understand what makes a human being a human being. (...) The solution to the problem of "what is a human being" can only come from an interaction between science, philosophy and sociology. Surely we need to understand what is the nature of man, before we can plan his appropriate society.

The intuitive and non-linear elements of my search for medical literature have already been described. Furthermore, I have come to realise that the complex topic of the prevention of disease cannot be a project for medicine alone. It certainly presupposes input from multidisciplinary teams. Therefore, I have made systematic attempts to integrate perspec-

tives and research methods from the humanities in this thesis. Also, simultaneously with my efforts to get acquainted with basic humanistic perspectives on 'the human condition' and health care, a series of academic gatherings involving both medical and non-medical scholars have had a strong impact on my learning, questioning and understanding. In particular, I want to mention the following academic events, which have come to represent milestones in the continuous reflective process that has resulted in this thesis.

In 2000, I attended the 2nd World Congress of Philosophy of Medicine in Krakow. This experience was a professional eye-opener. At the congress, I presented a lecture, based on a preliminary version of Paper I. Inspired by fruitful dialogues with medical colleagues and scholars from other disciplines, I returned to Iceland where I planned a Nordic workshop, titled *Human dignity in a medical context*. This workshop took place at Skálholt, Iceland, in the spring of 2001. It was attended by a multidisciplinary group of about 25 specially invited participants. Among them were members of *Filosofisk poliklinikk* ("Philosophical Polyclinic," founded in 1998, see www.uib.no/isf/filpol/) at the Faculty of Medicine, University of Bergen. *Filosofisk poliklinikk* has subsequently arranged four four-day multidisciplinary seminars at the Barony in Rosendal, Norway. I have had the opportunity to attend them all:

2002: Dignity and Dialogue: Exploring Medicine's Relational Foundations. The case history upon which Paper II is based was explored in-depth in a workshop at this seminar (see below).

2003: Health, Culture and Self. Exploring Modernity's Challenges to Medicine.

2004: The Meaning of Risk. Exploring the Foundations of Medical Evidence.

2005: The Power of Goodness. Exploring Help and Helplessness in a Medicalised Society. This seminar took place at the point where I was beginning to structure the discussion part of this thesis.

The Rosendal seminars have all been openly advertised and acknowledged by the Norwegian Medical Association as regular, continuous medical education courses. Each seminar has been attended by 25-30 people. *Filosofisk poliklinikk* has always paid minute attention to detail when the programme has been designed. This has resulted in learning processes which many experienced academics, in particular medical

doctors, have characterised as *a unique professional experience*. The academic content has been challenging, thought-provoking and controversial; opinions have been diverse, yet the atmosphere has always been utterly respectful.[107]

The seminars have – seen in retrospect – revolved around questions of moral responsibility in medicine. In order to make the implications of the concept of responsibility clear, one aim has been to develop the participants' understanding of the humanistic foundations of medicine. Icelandic professor of philosophy Vilhjálmur Arnason, twice a Rosendal participant, links this to what he calls a *relational responsibility in medicine*.[108] *Another* aim has been to stimulate reflection on the nature of the biomedical paradigm as we know it today. In particular, implications of the discourse on 'risk' and implementation of so-called 'evidence-based medicine' have been investigated. Arnason links this to the notion of *structural responsibility in medicine.*

The Rosendal participants have included medical doctors – many of them experienced general practitioners with research experience, philosophers, and academics from various non-medical disciplines. Among the specially invited external participant-lecturers at the Rosendal symposia have been Alfred Tauber, professor of medicine and philosophy in Boston; Arne-Johan Vetlesen, professor of philosophy at the University of Oslo; Kenneth W. Goodman, founder and director of the University of Miami's Bioethics Program; Iona Heath, general practitioner and chair of the BMJ ethical committee; Eric Cassell, US physician-writer and clinical professor emeritus of public health; Vilhjálmur Arnason, professor of philosophy at the University of Iceland; and Tor-Johan Ekeland, professor of psychology at the University of Bergen.

7.1.3 "Conversations with the situation"

The reflective process underlying this work should not be regarded in isolation from what I have experienced and learnt as an intern, during

[107] Readers familiar with medical culture are likely to know that new ideas are not necessarily treated with respect in the medical community. The history of Robin Warren and Barry Marshall, who were awarded the 2005 Nobel Prize for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease, is a reminder of this (see chapter 2.2.2). Eivind Meland, one of the co-founders of Filosofisk poliklinikk, has proposed the concept 'respectful dialogue' to describe an academic atmosphere where vulnerable and controversial arguments and ideas can be presented in the absence of arrogant or malicious critique.

[108] Arnason V. *Are we responsible for each other?* Lecture at the Rosendal seminar, 2005.

four years as a general practitioner in Norway, a short, but memorable, period as a resident at an oncology department, three years at the Department of Psychiatry at Landspitali University Hospital in Iceland, and five years as a staff physician in the same hospital, serving 4500 employees. My academic and clinical interests have ever more often come to interact and reinforce each other. For instance, my consultation office at Landspitali is sometimes the arena for what professor of education and development Donald A. Schön might have described as "conversations with the situation" (Schmidt 2000; Malterud 2001). That is to say, some of my patients at the hospital have taught me, as a professional, to see health and disease from a new perspective. These dialogue partners have often been experienced, devoted and previously healthy healthcare workers who have at some point encountered severe or recurrent health problems that have not found successful resolutions in the conventional, curative system of care. In these instances I have deliberately taken on a professional role distinctly different from that of a treating physician, co-reflecting with the person upon her biography and current life situation. I have realised that it can be quite unscientific, *and thereby unethical*, to address human disease and suffering only from the narrow perspective of conventional biomedicine. To put it another way, resistant suffering has become meaningful, and treatable, when the sick person's narrative and experience has come into focus. At this level, an 'existential logic' has become apparent (Kirkengen 2001 and 2005). For instance, I have seen how remarkably destructive the subjective experience of *humiliation and unfair treatment* can be to health.[109] What I have been able to contribute as a professional in these situations has first of all been an empathic recognition of the person's sense of violated dignity. I have subsequently made use of my growing understanding of 'doctoring-as-leadership' (Schei 2006). Thus, I have guided the person to focus on the resources and *possibilities of the situation*. I have written more about my experiences in this field in an essay called *Om mentorskap og medisin* (On mentorship and medicine, Getz 2003). In her thesis *The skapende mellomrommet i møtet mellom pasient og lege* ("The creative in-between in the clinical encounter"), Norwegian general practitioner

[109] This observation validates the theory put forward by previously mentioned Harvard researcher Jonathan Mann (1998). These individual stories are also congruent with the increasing number of studies which have (during the last 6-8 years) addressed the relation between *Organizational fairness (or justice) and health,* see Medline. Even when operationalised quantitatively, 'fairness' emerges as an independent determinant of employees' health and well-being. The most recent finding of the Whitehall study is that "justice at work may have benefits for heart health" (Kivimäki et al. Arch Int Med 2005; 165:2245-51). Other results from the Whitehall II study are listed in Appendix 4.

and researcher Eli Berg has explored successful cases of doctor-patient co-reflection along similar lines (Berg 2005). To sum up, my experience has taught me that the scientific base of the medical paradigm is simply not comprehensive enough for doctors to do a good job, and I see it as my professional responsibility to speak out about this.

7.2 Methodological information pertaining to the individual studies, not outlined in the published papers

7.2.1 Paper I

Exploration of the topic of anatomical soft markers for fetal chromosomal aberrations

Paper I contains an exploration of the development of the knowledge base related to *anatomical soft markers for chromosomal aberrations in the fetus* (see Paper I for definitions and explanations). The paper integrates numerical and hermeneutical approaches, as it aims to document and describe one particular chapter in the recent history of medical technology development. The paper can be regarded as both an analysis of very recent medical history and a contribution to the building of medical theory. As previously said, there is a very limited tradition within medicine for regarding *the medical knowledge base as such* as 'material' worthy of academic investigation. However, as I set out to describe the methodological approach that was used in Paper I, I found a publication by Trisha Greenhalgh and co-workers who describe a new scientific method, *the meta-narrative review* (Greenhalgh et al. 2005). This method refers to philosopher of science Thomas Kuhn's (1962) theory of scientific paradigms and was developed to address the diffusion of academic innovation throughout various medical and non-medical disciplines. I realised that the methodological approach in Paper I has many similarities to a meta-narrative review. The analytical process leading up to Paper I will therefore be presented with reference to the elements of the meta-narrative review, as outlined by Greenhalgh et al.

i. <u>"Territorial mapping" and "planning" phases (conducted in 1998-1999)</u>

- This was a period of informal dialogues about the potential academic relevance of investigating the topic of soft markers. These dialogues came to involve several trusted academic colleagues in various fields and resulted in a broad and open-ended outline of the research questions.

- During this period, general, broad and non-exhaustive searches related to the topic of prenatal diagnosis were conducted in PubMed®, the search engine of the National Library of Medicine. I applied various combinations of search terms including: screening, ultrasound, fetal/foetal, pregnancy, trimester, soft marker, Down's/Down syndrome, trisomy, anomaly, ethics.
- An initial exploration was made of the particular issue of soft markers, by "browsing" the internet and performing preliminary targeted searches in PubMed.
- Contact was established with fetal medicine experts in order to gain access to information and interpretations that could not be retrieved from the published peer-reviewed literature. A further description of this collaboration appears below (marked with *).
- I was allowed to spend three working days at the National Centre for Fetal Medicine in Norway (1999). The visit involved observations of clinical practice and collegial discussions related to this.[110] At this centre, clinical dilemmas related to fetal soft markers in the second trimester of pregnancy were encountered on a daily basis at the time.

ii. "Search" phase (mainly conducted in 1998-1999)

- This phase involved comprehensive, targeted searches using the specific terms related to anatomical soft markers in PubMed (see further comments below, marked with**).
- Subsequent searches were made for additional empirical papers by way of manually searching selected journals and 'snow-balling', i.e., searching references for references, and pursuing the publication list of key researchers and clinicians.
- A continuous e-mail dialogue was maintained with my main fetal medicine expert informant, to ensure that no important publications were missed.

iii. "Mapping" phase (mainly conducted 1998-2000)

- This phase involved identification of conceptual, theoretical and methodological key phenomena of the research area in question.
- Identification of key actors and events in the unfolding of the re-

[110] I had been granted the necessary permissions to enter the National Centre for Fetal Medicine as a researcher, as it was part of my original research protocol to observe clinical encounters and interview expectant mothers as well as their clinicians in this setting.

search tradition was a key issue, including scientific milestones and seminal papers related to the anatomical soft markers.
- Attention was paid to the prevailing language and reasoning used by scientists to 'tell the story' of their scientific work and/or clinical practice.
- The above-mentioned e-mail dialogue was maintained to ensure that my interpretation of technical details remained valid.

iv. "Appraisal" and "synthesis" phases (1999-2000)
- Each primary paper/study retrieved by searching the literature was examined with respect to its validity and relevance to the study in question.
- Key results of relevant publications were extracted, and comparable studies were viewed together. The chronology of the development of the research field related to soft markers was gradually outlined.
- The numbers of original publications related to each of five selected soft markers were counted as a function of time. This made it possible to illustrate visually how the research field surrounding the anatomical soft markers developed. This way of describing the development within a research field appears to be a core element of the meta-narrative review process.
- Through reflection and dialogue with my co-author, a preliminary synthesis of the emerging findings and their implications was now prepared. Further literature searches were driven by this reflective process. They came to involve a wide range of topics, such as maternal-fetal bonding, fetal development, the vulnerable child syndrome, shortcomings of the principlistic bioethical paradigm, feministic theory, papers on the value-ladenness of medical technology, etc.
- Through continued reflection and correspondence with selected scholars regarding particular aspects of the paper, a final synthesis of the findings was formulated.

v. "Recommendation" phase (2000- 2001)
- The overall messages from the meta-narrative review were formulated. Implications for practice, policy and further research were outlined. The paper was subsequently submitted to *Social Science & Medicine*, where it was subjected to review by three experts in the field of prenatal diagnosis.

* *Contact with external experts:* In order to ensure overview of and valid interpretation in fetal medicine, Kjell Å. Salvesen, MD, PhD at Nasjonalt senter for fostermedisin (the National Centre for Fetal Medicine) in Trondheim, Norway, made himself available for consultation by e-mail throughout the whole study period. This contact was essential since very limited published information could be obtained on the issue of how soft markers were handled in daily clinical practice throughout the Western world. Salvesen described the clinical "golden standard" at 'his' competence centre but also had insight into how the topic was handled internationally, based on unpublished information and dialogues with clinicians and scientists in the small and well-defined international fetal medicine expert community. In addition to Salvesen, Prof. Martin Whittle of the UK, who expressed concern in relation to what he saw as soft marker dilemmas in 1997 (see reference list in Paper I), was contacted. This resulted in several acquaintances, most importantly with UK psychologist Catherine Baillie. She had recently completed original research (then still unpublished) on parental experience in relation to the soft marker dilemmas. Baillie's work (see Paper I) became an empirical cornerstone for the analysis in paper I.

** *Formal literature search on the topic of soft markers:* As part of the review of the relevant literature, a formal, computerised search related to the five most researched soft markers was conducted through PubMed®, the National Library of Medicine's (NLM™) journal literature search system. This was done to illustrate that Paper I is about the rise and development of a distinctly new body of medical knowledge: figure I in Paper I depicts the number of published original papers about the five most commonly discussed soft markers graphically as a function of time, from the time the topic first appeared in the biomedical literature shortly after 1980 until 1999, the year preceding the year when the systematic literature searches were conducted. Several search terms for each of the relevant soft markers were applied, as the terminology tended to change over time. An example: The soft marker, currently termed "nuchal translucency" (referring to the first trimester of pregnancy), was originally described in the second trimester of pregnancy where it was termed "nuchal oedema", "nuchal thickening" or "nuchal fold". In addition to the specific search for each individual soft marker, more informal methods were used. As the fetal medicine expert community appeared to be small, the names of the 10-15 most active authors

were systematically used to cross-check for additional relevant papers. In addition to the search in PubMed, reference lists of all key references and seminal papers were checked to identify papers that might have been missed by the computerised search. Very few (in the range of 5-10 in total) additional papers were identified in this way. The number of retrieved original articles for each marker per year was always within such limits that it was possible to keep a list of them and check that each of them was relevant. Thereby, it was assured that no publication was counted more than once.

7.2.2 Paper II

Development of a case history to be submitted to critical analysis

Paper II is an analysis of a case history which can be found in the introduction to the paper itself. The case can be traced back to an authentic consultation in the office of an experienced general practitioner (GP) in Trondheim in 2001. It was a clinical encounter which evoked professional uneasiness in the GP, despite his knowing that he had handled the case 'correctly', according to the golden standard of evidence-based medicine (EBM). The GP recounted the essence of the case – as he saw it – to two academic colleagues at the Department of Public Health and General Practice at the Norwegian University of Science and Technology (NTNU). The department was responsible for the planning of the 12th Nordic Congress for General Practitioners, and I was subsequently invited to contribute to a plenary lecture which was to address the dilemma recounted by the GP. My task was to provide 'contra EBM' arguments, as opposed to the 'pro EBM' speaker who would present the 'evidence-based' and thereby presumably the correct way to handle the situation. I thereby had to search for theoretical arguments and scientific data to support the GP's reported perception that the consultation had in a sense been *burdened by*, rather than *supported and facilitated by*, biomedical 'evidence'.

A discussion of the use of an anonymised case history as 'material' for critical reflection and theory development is warranted. This is not a common approach in medical science. As medical doctors we are familiar with cases that present new disease entities or syndromes, unexpected therapeutical side effects and other complications, etc. In these contexts, case studies are typically considered as contributing most to science when little is known about a phenomenon. Case studies are typi-

cally regarded as a first step in the development of medical knowledge, and decreasingly useful as more knowledge accumulates (Anderson et al. 2005). It has however been demonstrated in other contexts, that case studies can be appropriate for exploratory, descriptive, or explanatory purposes at any level of knowledge (Anderson et al. 2005). The relevance of appreciating evidence that emerges *in the context of a particular clinical encounter* has also been highlighted by Kirsti Malterud, who stated (2002):

> Regarding the clinical encounter as constitutive of medicine, the specific knowledge generated in this encounter deserves status as evidence. So far, such issues are nearly invisible on the conventional maps of EBM. (…) If medicine insistently discards clinical knowledge from the realm of valid evidence, clinical practice will be isolated from scientific knowledge and medicine will lose its credibility as a scientifically based professional activity.

The use of casuistries, fictional and factual narratives or stories has long since been acknowledged as important to understanding and theory development in medical ethics (Jones 1999). Reflections on case histories also hold a central place in Donald A. Schön's investigations of how professional practitioners, such as medical doctors, learn and develop their skills. Influenced by existential philosophy, Schön affirms "the here-and-now as the test, the source, the limits of knowledge". Theory building must grow out of the concrete things happening here and now, be tested against it, and then tested against the next situation, which may turn out to be different. Schön points out how stories can play a useful role in many kinds of academic research (Schmidt 2000).

In a recent editorial, Greenhalgh (2005) reflects upon the use of 'anecdotes' as a basis for medical research. She states that narratives suitable for research purposes tend to have three defining features:

1. an account of the unfolding events over time,
2. 'emplotment', i.e., the rhetorical juxtaposition of events to convey meaning, motive and causality, and
3. 'trouble', i.e., a breach from something that was expected.

Trouble, Greenhalgh says, "is the raw material from which plot is woven", i.e., the point of departure for further investigation. The case in Paper II satisfies Greenhalgh's *trouble criterion*: the clinician feels that he may have done something wrong in relation to the patient, despite having done everything *right* in terms of evidence-based medicine.

Case histories represent flexible frameworks for discussion and provide a tool for studying what Anderson et al. (2005) call integrated systems: every case story contains a human story as well as a medical story, which together can highlight various aspects of "person management, case management, health system management, and self-management" (Cox 2001). The presentation of any particular case, however, is never 'objective' or 'true'; every case history reflects the basic assumptions, values and intentions of its author(s). *Like any other set of narrative or numerical material, it imposes a context upon the reader* (Carson 2005). According to Greenhalgh, the validity of any given case should be judged by narrative criteria; the crucial question is whether the story rings true and appears authentic and credible to the reader/listener.

Case stories have previously proven to be useful tools for highlighting the particular distinction between *evidence-based medicine*, where data are derived from population studies so as to feature the characteristics of a theoretical and non-existent 'mean' individual, and *narrative-based medicine* which focuses on one particular individual's experience (Bleakley 2005). It is generally presumed that good doctors knowing 'the art of medicine' are able to integrate both perspectives in any given clinical encounter. The case in Paper II was purposefully constructed[111] (or "packed", in the terms of Carson) to stimulate further reflection on the task of integrating EBM and humanistic perspectives in the clinical setting. The case can be seen as extreme in the sense that the 'scientific' (EBM) approach and the narrative-based approach turned out to represent two kinds of 'knowing' about the patient that were mutually exclusive. But in this respect, the case is authentic. The fact that "the science" and "the art" of medicine no longer went hand in hand but pulled the clinician's mind in opposite directions was the very reason why the experienced GP brought this particular case to the academy. In a sense, the case can be regarded as an *anomaly*[112] in Thomas Kuhn's terminology (1962).

At the 2002 Rosendal seminar, two months prior to the scheduled plenary session at the Nordic congress for general practitioners, the case history in Paper II was discussed in a multidisciplinary group. Interest-

[111] A different secondary version of the same primary case was developed by Irene Hetlevik for use in the Norwegian textbook of general practice. See Hunskaar S (red). *Allmennmedisin*. Oslo: Gyldendal akademisk. 2003, p. 780.

[112] An anomaly is an irregularity that is difficult to explain using existing rules or theory. See Appendix 2.

ingly enough, Trisha Greenhalgh encouraged critical reflection upon the task of implementing EBM in clinical practice in this same year (2002) when she stated that:

> The enduring tradition of 'Balint groups'[113] indicates that storytelling and reflective discussion in groups is a time-honoured method for professional development. (...) The evidence-based Balint group is surely the epistemological marriage we have been waiting for.

The case evoked intense debate at the Rosendal seminar. The discussion even came to involve an accompanying person (a renowned historian) who was not present at the workshop itself (see Table III in Paper II). Some of the participating doctors initially responded to the case history with clear frustration; they did not see that the case presented a dilemma worth discussing at all. Other participants responded with silence. But as time went by, the atmosphere changed. The turning point came when a professor of philosophy who had listened to the debate in silence, stated that he saw a clear ethical dilemma related to EBM as the only defendable approach to the man who was described in the case. But the best argument he could find to support his view was not part of his academic knowledge, he said. It came from his personal experience in relation to his own mother, witnessing her as she aged.[114] It thereby appeared that the case history could serve as a catalyst for radical and non-linear reflection upon the challenge of practicing "narrative-based medicine in an evidence-based world" (Greenhalgh 1999).

Agreeing upon a working definition of EBM for the 'pro et contra' analysis
Part of the material that was subjected to critical analysis in Paper II was "the body of authoritative biomedical knowledge fulfilling the criteria as being 'Evidence-based medicine', i.e., the golden standard for good clinical practice. As outlined in the introduction, the working group behind the EBM-movement maintained that the concept of evidence should be understood in a broad sense: "EBM is the conscientious, explicit and judicious use of current best evidence in making decisions about the individual patient" (Sackett et al. 1997). As explored in the previous theoretical section, however, the mainstream interpretation of EBM has become a far more narrow and authoritative one (Hetlevik 2004). EBM does not involve evidence related to interpretation of the

[113] The works of psychoanalyst Michael Balint (1896-1970) are mentioned in the theoretical introduction to this thesis. Reflective "Balint groups" and societies are still active internationally.

[114] Recounted with permission.

particular patient's situation, only evidence that pertains to choosing optimal interventions, as documented by

1) randomized, controlled trials and meta-analyses for assessing the efficacy of interventions, and
2) epidemiological studies of the specific disease condition in question for predicting the course of illness, and, on a meta-perspective:
3) clinical guidelines provided by expert committees that have compiled and evaluated evidence in categories 1 and 2.

This narrow interpretation of EBM was submitted to critical analysis in Paper II. In relation to preparation of the manuscripts, it was evident that the pro-EBM author (PN), the contra-EBM author (LG) and the organising and facilitating academic-clinician (IH) interpreted the notion of EBM in the same way.

7.2.3 Paper III

This paper is a focused, critical appraisal of the well-established tradition for doctor-initiated, individually oriented preventive measures in the context of the clinical consultation (Stott and Davis' model, see reference list in paper III). The paper scrutinises an original problem, i.e., to what extent the honoured argument for opportunistic preventive initiatives remains valid, as we start aggregating – in the clinical encounter – a series of recommendations that have been derived in different research contexts. From a methodological point of view, the paper resembles analytic research papers in the area of medical ethics and philosophy. The aim of the paper is however not to provide an exhaustive overview of relevant theory and research related to opportunistic preventive interventions, but to highlight a distinct set of practical and ethical dilemmas which are bound to arise in primary healthcare settings where all clinical recommendations will ultimately converge. The discussion of this thesis will demonstrate that Paper III holds a logical and necessary position among the five sub-studies. It highlights one of the suggested core elements of a sustainable and responsible preventive medicine, namely the notion of equity (see chapter 9.5).

7.2.4 Papers IV and V

Pilot study to strengthen our motivation to conduct the studies

The main reason why we wanted to perform the studies that resulted in

Papers IV and V of this thesis was that, based on former studies (Hetlevik 1999), we had good reason to believe that implementation of the *2003 European guidelines on cardiovascular disease prevention in clinical practice* would result in a very large proportion of the population being labelled as having an unfavourably high blood pressure, cholesterol, or combined disease risk level. Whilst preparing our formal investigation of the HUNT 2 data, we were allowed by Professor Emeritus of General Practice Calle Bengtsson to perform some preliminary calculations on data from the Population study of women in Gothenburg, Sweden (Bengtsson et al. 1997). The results indicated that our concerns were warranted. So our research group went on to formally analyse the data from the HUNT 2 study.

The Nord-Trøndelag Health Study (HUNT)
This study so far consists of the two cross-sectional sub-studies HUNT 1 (1984-6) and HUNT 2 (1995-7). HUNT 3 will start in 2006. HUNT is one of the largest health studies ever performed. It contains a database of personal and family medical histories, collected in two consecutive cross-sectional studies. It also contains a bio-bank. The main objectives have been related both to epidemiological and clinical research. The HUNT 1 and 2 studies have been approved by the Data Inspectorate of Norway and by the Regional Committee for Medical Research Ethics, and all information from HUNT is treated according to the guidelines of the Data Inspectorate. The participation has been based on informed consent. The design and questionnaires applied in the HUNT study is further presented on the study's website: http://www.hunt.ntnu.no. Holmen and co-workers have also published a comprehensive overview paper describing the HUNT study (in English) in the journal *Norsk Epidemiologi* (2003).

The population in Nord-Trøndelag County is stable and well defined. The geographical, demographical, and occupational structure and patterns of morbidity and mortality are considered fairly representative of Norway as a whole. The county, however, lacks a large city, and the average level of education is somewhat lower than the national average, as is the average income.

Some particular issues relating to The Nord-Trøndelag Health Study 1995-1997 (HUNT 2) should be mentioned: All residents of Nord-Trøn-

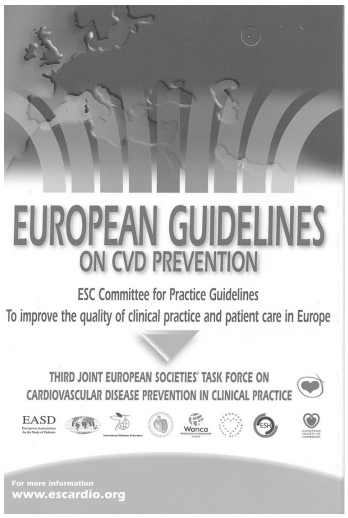
delag County, aged 20 (reaching their 20th birthday during the year of screening in their municipality) and older were invited to the health survey between August 1995 and June 1997. The invitation letter was sent by mail attached to a three-page questionnaire (Questionnaire 1, see the HUNT website and Appendix in this thesis) and an information folder. The questionnaire was to be completed and returned at the screening site. A second questionnaire (Questionnaire 2, see the HUNT website and Appendix) was handed out at the screening site to be completed and returned by mail. In total, the HUNT 2 (1995-1997) study recruited 30 860 men (67% of those invited) and 35 280 women (76% of those invited), aged 20 and older.

The 2003 European guidelines on cardiovascular disease prevention in clinical practice

All the necessary information regarding the guidelines (De Backer et al. 2003) is presented in Papers IV and V. However, it might be of interest to see how the guidelines are presented on the homepage of the European Society of Cardiology.

Figure 7.2.4 The front page of the 2003 European Guidelines on the European Society of Cardiology (ESC) website (www.escardio.org). Note that pocket and PC versions for personal use can be ordered. Accessed April 19th 2005.

European Guidelines on Cardiovascular Disease Prevention in Clinical Practice



Document type: Guidelines & Scientific Statements

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8. RESULTS

8.1 Synopsis of Papers I-IV

Paper I
Ultrasound screening of pregnancy: Advancing technology, soft markers of fetal anomaly and unacknowledged ethical dilemmas.
Getz L, Kirkengen AL. *Social Science & Medicine 2003*; 56:2045-57

The paramount objective of the project, of which the present investigation constitutes the first part, is to contribute to critical reflection and theory development in medicine by systematic documentation, analysis and conceptualisation of unacknowledged ethical dilemmas arising from clinical implementation of advancing, preventive, individually targeted medical technology. This paper addresses the topic by exploring the relation between advancing ultrasound imaging technology, the identification of *soft markers for fetal chromosomal aberrations* in the unborn child (in particular trisomy 21 or Down syndrome), and the rise of novel ethical dilemmas, with reference to the period 1980-2000.

Material and methods
The material analysised was the evolving biomedical knowledge base and clinical practice related to anatomical soft markers for fetal chromosomal aberrations. More specifically

1. a comprehensive literature review was performed by a combination of formal and informal searching methods. This review covered the relevant biomedical literature but also extended into the social sciences.
2. information which was inaccessible by other routes was obtained by consultations with national and international experts who contributed unpublished interpretations and knowledge pertaining to the issue of soft markers.

Results and implications
The principal result of the study was formal documentation of the fact that the practice of routine fetal screening by obstetrical ultrasound, applying the latest in diagnostic equipment, appears to have caused harm to an unknown number of expectant parents and unborn children dur-

ing the period covered by the study. This harm involved loss of an unknown number of healthy fetal lives as well as significant distress in an unknown number of expectant parents. This resulted from the fact that many ultrasound examiners had to counsel pregnant women about an increased risk for fetal chromosomal aberrations on the basis of subtle findings in the ultrasonographic image, interpretations that proved to be misleading as solid scientific evidence on the significance of the findings accumulated at a later date. Profound and private moral dilemmas thereby emerged as a direct consequence of application of an advancing medical technology in a routine clinical setting. The study thereby challenges the bio-medical tradition for considering scientific knowledge production as a value-neutral act per se. It also provides strong arguments for scrutinising the interface between prenatal testing and human experience, and the relevance of applying scientific methods and ethical approaches extending beyond traditional biomedicine and bioethics.

Paper II
A matter of heart. The GP consultation in an evidence-based world.
Getz L, Nilsson P, Hetlevik I. *Scandinavian Journal of Primary Health Care* 2003; 21:3-9.

This second paper addresses unacknowledged ethical dilemmas arising from clinical implementation of evidence based medicine (EBM) in the individual consultation. It explores the inherent tension that may arise between EBM and a so-called humanistic approach.

Material and methods
The material which was subjected to scientific analysis consisted of

1) an authentic *case description* brought to the academy by an experienced general practitioner. The clinician reported professional uneasiness in relation to the consultation, despite having treated the patient 'correctly' according to the standards of evidence based medicine.
2) the body of *evidence based medical (EBM) knowledge* pertaining to the above-mentioned case at the time of the study (2002).
3) relevant theories and *scientific knowledge beyond conventional EBM* that could support the GP's sense of professional uneasiness in relation to the case.

Results
The study documented that the clinician could find substantial theoretical support for professional uneasiness related to the implementation of EBM in the particular consultation in question.

The conventional EBM literature indicated that persons with a previously unrecognised myocardial infarction (MI) ought to be treated like patients with a history of a symptomatic MI. The incidental finding in the ECG should thereby be communicated to the person, accompanied by an offer of further diagnostic testing, risk evaluation, and follow-up with life-style interventions and up to four different medications. Further critical evaluation of the EBM literature, however, revealed that the quantity and quality of evidence concerning the natural prognosis and potential intervention benefits for an 'average' 70-year-old man with a previously unrecognised MI was far more limited than could be expected from the term "evidence-based medicine".

Beyond conventional EBM, substantial scientific evidence could be found on the relation between experience of meaning and physiological processes in the body. For instance, there appears to be a clinically significant relation between self-perceived health and survival. There is also considerable evidence of a direct link between negative emotions and cardiovascular disease progression. Scientific knowledge about how people/patients perceive being labelled as "at risk" for future disease events was almost non-existent in 2002.

Implications of the findings
A *truly evidence-based* approach to the person in the case would encompass theories and knowledge that extend beyond the paradigm of conventional EBM. The analysis also indicated that the bioethical principle *respect for patient autonomy* can have fundamental limitations in relation to the paradigm of EBM. It also appeared that in this particular case, application of conventional EBM (which would be in favour of intervention) and other kinds of relevant medical evidence (that could be used as arguments to refrain from intervention) turned out to be mutually exclusive kinds of scientific knowledge. In total, there were so many scientific uncertainties relating to this particular individual that they might represent an argument for following the ethical principle *do no harm* and not interfering with the patient's life and self-image.

In total, the study challenges the bio-medical tradition for considering implementation of medical evidence and communication about risk as value-neutral acts *per se*.

Paper III
Is opportunistic disease prevention in the consultation ethically justifiable?
Getz L, Sigurdsson JA, Hetlevik I. *British Medical Journal* 2003;327:498-500.

This third paper addresses the topic of unacknowledged ethical dilemmas arising from clinical implementation of advancing medical technology by exploring the aggregated impact of advancing preventive technology in the form of authoritative clinical guidelines and checklists on everyday clinical practice in primary health care. Paper III can be seen as a general elaboration of some particular topics that were raised in paper II.

Material and methods
The setting analysed is the consultation in general practice (primary health care, family medicine). The material analysed consisted of

1) A widely recognised *consultation model* by Stott and Davis (1979), particularly emphasising the clinical task of "opportunistic health promotion."
2) The aggregated body of *EBM-based clinical checklists and guidelines* which primary healthcare clinicians are implicitly expected, or explicitly advised, to implement in their daily practice, in accordance with the above-mentioned consultation model.
3) Theories and scientific knowledge extending beyond the paradigm of conventional EBM indicating a need to reconsider the moral foundation for opportunistic implementation of preventive guidelines in routine clinical practice.

Results and implications
The paper highlights that the number and complexity of potential preventive interventions that can be considered relevant, opportunistic initiatives have increased dramatically during the last decade. Risk communication and decision-making in relation to preventive interventions have become a correspondingly demanding task.

The rapid increase in doctor-initiated, opportunistic preventive actions and check-list driven medicine may gradually come to repress or divert an open dialogue between patients and doctors. This general development should be considered in light of the principle of *respect for patient autonomy.* The scientific 'truth' in relation to human health reaches far beyond the scope of evidence-based medicine. It can be argued that it is ethically questionable to impose evidence based preventive interventions on patients who do not express explicit interest in undergoing this particular kind of medical evaluation.

The paper sheds new light on medical doctors' limited adherence to clinical guidelines in the preventive sphere. This phenomenon, which has been called *clinical inertia*, may perhaps reflect unacknowledged ethical dilemmas arising from the doctor's steadily expanding preventive medical agenda.

Paper IV
Ethical dilemmas arising from implementation of the European guidelines on cardiovascular disease prevention in clinical practice: descriptive epidemiological study.
Getz L, Kirkengen AL, Hetlevik I, Romundstad S, Sigurdsson JA.
Scandinavian Journal of Primary Health Care 2004;22:202-8.

This is the first of two papers addressing the topic of unacknowledged ethical dilemmas arising from clinical implementation of advancing medical technology by modelling the practical impact of implementation of the *2003 European guidelines on cardiovascular disease prevention in clinical practice* in an unselected population. In this paper, there is a focus on the single risk factors serum cholesterol and blood pressure (BP).

Material and methods
The *2003 European guidelines* were applied to a cross-sectional population study comprising 62.104 adult Norwegians, aged 20-79, who participated in The Nord-Trøndelag Health Study 1995-97 (HUNT-2). Total, age- and gender-specific point prevalences of individuals with total cholesterol ≥ 5 and/or systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or taking antihypertensive medication was calculated and the results critically reflected upon.

Results and implications
In total, 76% of individuals, aged 20-79, appeared to have an 'unfavourable' cardiovascular disease risk profile, according to guideline definitions of optimal blood pressure and serum cholesterol. The point prevalence of individuals with cholesterol and/or blood pressure above the recommended cut-off-points increases with age. By age 24, the prevalence reaches 50%. By age 49, it reaches 90%. It has thereby been documented that implementation of the *2003 European guidelines on CVD prevention in clinical practice* would label a large majority of Norwegian adults as having an unfavourable cardiovascular disease risk profile. Important ethical dilemmas arise at the point of guideline implementation, relating to risk labelling and medicalisation, as well as resource allocation and sustainability within the healthcare system.

Paper V
Estimating the high risk group for cardiovascular disease in the Norwegian HUNT 2 population according to the 2003 European guidelines: modelling study.
Getz L, Sigurdsson JA, Hetlevik I, Kirkengen AL, Romundstad S, Holmen J. *British Medical Journal* 2005;331:551-4.

Note: this paper exists in a short version (published in the paper journal) as well as a full text version (accessible from the bmj website). The full text version is enclosed with this thesis: doi:10.1136/bmj.38555.648623.8F (published 15 August 2005).

In this second modelling paper, the size of the "high risk" group, as defined by a *combined risk estimate*, is calculated and discussed. This is the group which should receive "maximal clinical attention", according to the *2003 European guidelines on cardiovascular disease (CVD) prevention in clinical practice.*

Material and methods
The *2003 European guidelines* were applied to a total of 5.548 participants, aged 40, 50, 55, 60 and 65, who participated in The Nord-Trøndelag Health Study 1995-1997 (HUNT-2), Norway. These are the same age groups that are depicted in the SCORE risk chart that is part of the guidelines. The distribution of risk categories for CVD was calculated, with emphasis on the "high risk" group; i.e., ≥5% probability for a fatal CVD event within 10 years.

Results and implications

Application of the 2003 European guidelines on CVD prevention in a well-defined Norwegian population would label four out of ten women and nine out of ten men, aged 50, as "at high risk for fatal cardiovascular disease". No men, aged 40 or older, would be classified as "at low risk for fatal CVD". Already by age 40, 23% (95% confidence interval 19-26) of women and 86% (83 to 89) of men are at "high risk", according to the guidelines. At age 50, the "high risk" category includes 40% (36 to 43) of women and 89% (87 to 93) of men. At age 65, the numbers are 84% for women (81 to 87) and 92% (89 to 94) for men. Implementation of the guidelines would thereby classify the majority of adult Norwegians as "at high risk for fatal CVD" and, thus, eligible for "maximal clinical attention". This finding raises important scientific questions related to the evidence base of the guidelines, as well as questions related to the professional process leading up to the publication of these authoritative guidelines. It also predicts major ethical dilemmas related to resource allocation, workload and medicalisation. A discussion about the fundamental values, strategies, and sustainability of preventive medicine appears to be warranted.

8.2 Overview of results and emerging topics

In the following table, an attempt has been made to give an overview of the topics that are dealt with in the five papers of this thesis.

TOPICS	PAPER NUMBER				
	I	II	III	IV	V
Issues related to the theoretical foundation of contemporary, individually based, preventive medicine					
The value-ladenness of biomedical science and practice	√	√	√	√	√
The limitations of the theoretical foundation underlying contemporary Western biomedical research and practice	√	√	√	√	√
The potential for unintended or unrecognised harm related to the implementation of new, preventive medical technology in routine clinical practice	√	√	√	√	√
The problems and dilemmas related to identifying risk for future disease or disability, given a physiological link between human experience of meaning and physiological state (extended to the maternal-fetal unity in Paper I)	√	√	√	√	√
The need to reconsider and revise the theoretical foundation underlying preventive medical activities directed towards individual persons/ patients	√	√	√	√	√
The strengths and limitations of the methodological approach leading up to 'evidence based medicine'	√	√	√	√	√
The emergence of EBM as a contemporary and indisputable authoritative value in medicine	√	√	√	√	√
Blurring of borders between 'population health care' initiatives and personal health care in the consultation	√	√	√	√	√
Topics inherent to the particular paradigm of EBM					
Dilemmas related to risk communication and risk-related decision-making	√	√	√	√	√

To be continued on the next page...

	I	II	III	IV	V
The dilemma of implementing evidence derived from groups on the level of the individual	√	√	√	√	√
Dilemmas related to application of the principle of patient autonomy in relation to the paradigm of EBM	√	√	√	√	√
The application of biomedical evidence in inappropriate clinical settings; i.e., transposing experimental data emerging from high risk populations in other clinical settings	√				√
The problems related to cut-off points for estimating and categorising risk					
– applying single risk factors	√			√	
– applying combined risk estimates	√				√
Dilemmas related to medicalisation of populations	√		√	√	√
Issues related to practical sustainability and carrying capacity of the healthcare system					
The practical processes and procedures related to development and implementation of clinical guidelines and recommendations	√		√	√	√
The practical feasibility of preventive interventions in terms of workload and resource allocation			√	√	√
The need to regard national/local preventive medical activities from a global perspective	(√)		(√)	√	√
Meta-perspectives					
The danger of alienation of patients and healthcare professionals from the basic premises of human existence by technological 'enframing'	√	√	√	√	√
Doctors' limited adherence to clinical guidelines in the preventive sphere		√	√	√	√
The recognition of professional responsibility in relation to both scientific *bringing forth* and *practice* of medical knowledge	√	√	√	√	√

9. DISCUSSION AND IMPLICATIONS

This thesis started with the definitions and goals of medicine and contains an exploration of three concrete clinical arenas with reference to six theoretical knowledge fields. All five papers highlight that implementation of new, preventive medical technology at the interface between individually and population-oriented care can lead to the emergence of important and complex ethical as well as practical dilemmas and even have harmful consequences. This implies that technological innovations in preventive medicine should be more systematically and comprehensively analysised than they recently have been. However, evaluating each particular new technology is not enough. At the same time, the overall goals, means and priorities of preventive medicine should be made clear, explicit and accessible to scrutiny and debate (McKee and Raine 2005; Roberts and Reich 2002).

All five papers in this thesis clearly show that preventive medical research and practice must be regarded as value-laden activities. And it has, during the process of writing, become increasingly clear to me that the theoretical foundation presently underpinning these activities does not encompass the human condition in a scientifically comprehensive manner, and this shortfall renders the foundation ethically untenable. As I approach the completion of this thesis, I realise that my main concerns, and the main topic of this thesis, can be seen as representing a contemporary affirmation of Martin Heidegger's and Hans Jonas' conceptualisations of the *dangers related to technological enframing of the human condition* (see chapters 2.4.2, 4.1.4 and 4.1.6). And once this is said, it follows as a logical consequence that all the papers in this thesis point to the relation between the development and implementation of new technology, on one side, and moral responsibility of medical researchers, administrators and clinicians, on the other.

9.1 Medical responsibility - promoting just and fair health care

Canadian professor of sociology Arthur Frank has recently remarked how the noun form of "medical ethics" appears to suggest something substantive, embedded in a body of principles designed to help solve recognizable problems in clinical practice, and located in the offices of institutionalized experts called "ethicists" (Frank 2004). As an exten-

sion of this way of conceptualising ethics, Frank suggests that we start to think about ethics in terms of a *process* of lives and decisions affecting each other over time. He believes that most clinical dilemmas arise as a consequence of prior actions and decisions made by ourselves or others – i.e., any decision *now* is part of a process that began *then*. An important potential of ethics in medicine is found outside the domain of institutional ethics as a prescribed procedural activity; it lies in our '*being ethical*' in everyday thought and practice. In Frank's opinion, being ethical has less to do with making single decisions than with initiating and maintaining a process of constructive events (Frank 2004). I agree. As a community of medical researchers, administrators, opinion leaders and practitioners, we need to conceptualise and develop a distinct awareness of how we all contribute, day by day and step by step, to "*the arrival of things into existence*"; i.e., to the making of medical reality. As Heidegger and Jonas taught (see chapter 4.4.4), we need to rediscover the link between causality and moral responsibility. This link was obvious to the ancient Greek scholars but has since become obscured in a society which has learned to regard the creation of new knowledge and technology as a value-neutral activity that can and should be pursued for its own sake.

In the concluding chapter to the previously mentioned *Goals of medicine project*, titled *Looking forward* (Callahan 1996), the writing group formulated a series of recommendations. The chapter opens by acknowledging that "the traditional, powerful and attractive strong premises" underlying modern medicine have been a source of great advances. Now, however, it seems to be time to re-examine these premises as they imply an increasingly naive and resource-consuming faith that medicine will ultimately win the war against its two main enemies – disease and death. The Goals of Medicine project group's advice is that the medical community should learn to think more along the lines of ecology. This would imply becoming more *temperate, prudent, economically sustainable, just and equitable, socially sensitive, and respectful of genuine human choice and dignity* (Callahan 1996). In many respects, these key recommendations are congruent with the central conclusions of Papers I–V in this thesis. In total, preventive medical research and practice should become somewhat more directed towards those conditions of human life that are health preserving and enhancing and a bit less preoccupied with fighting disease and death.

As medical doctors, we have been proud of our professional rights and duties to serve as "a self-directive, moral community" (see chapter 4.1.1). In this context, our right to define and direct production and implementation of new medical knowledge has been regarded as a self-evident part of our professional autonomy. However, as outlined by others (see chapter 4.1.1), the professions are, in general, (May 2001) and the medical profession, in particular (Horton 2005), under siege, and it seems quite probable to me that the credibility, influence and autonomy of the medical profession will continue to decline if people do not acknowledge that our priorities and activities are just and fair.[116] For instance, I believe that the approach to disease prevention and health promotion which is embedded in the 2003 European guidelines on CVD (the topic of Papers IV and V) ought to be evaluated from this viewpoint. The underlying idea, to prevent as much disease as possible in a given population, appears *rational* in its own right. But within a system with limited resources, which will always be our clinical reality, it does not seem reasonable and *fair* to embark on such an out-reaching project without even considering beforehand how the healthcare system is going to accommodate the guidelines, and how their implementation might come to affect services for people who are already asking for our help, or who might benefit from other preventive services. At this point, it may be relevant to evoke the teachings of Harvard philosopher John Rawls (1921-2002), one of the most influential political philosophers of the 20th century. After authoring the seminal book *A theory of Justice* in 1971, Rawls continued outlining the essence of his key concept called "justice as fairness." His final theory appeared as *Justice as fairness: a restatement* in 2001. It outlines a theory of justice based on the idea of a social contract, as a fair system of cooperation, based on reciprocity and mutuality and the notion of what is good for each participant. Rawls emphasised the importance of maintaining the social bases of self-respect and self-confidence among people in general and scrutiny of how political decisions would affect the least advantaged in society in these important areas. Rawls' theory was not primarily designed to address issues of health care, but it has been applied by other thinkers as a guide to analysing the organisation of health care, both nationally and

[116] *Just*: from Latin *justus*, from *jus* right, law; akin to Sanskrit *yos* welfare. It implies having a basis in or conforming to fact or reason, being faithful to an original, acting or being in conformity with what is morally upright or good (Merriam-Webster 2005). *Fair*: from Old English *fæger*; akin to Old High German *fagar* beautiful: marked by impartiality and honesty, free from self-interest, prejudice, or favouritism. Conforming to the established rules. Consonant with merit or importance. Open to legitimate pursuit, attack, or ridicule (Merriam-Webster 2005).

globally (Horton 2003, Ruger 2004 i and ii). Furthermore, continuing from Rawls' argument, one might also address the medical knowledge paradigm from the perspective of "justice as fairness": one of the major challenges facing modern medicine today is to conceptualise, develop and implement knowledge about the causal pathways through which socioeconomic and other inequalities work to produce gradients in health outcomes, whether regarded on a local, national or global level (see chapter 2.1.4). This is also the claim of a group of US scholars that sees Rawls' theory as a compelling tool to help re-direct academic and clinical attention (Daniels et al. 2000). They state:

> With some significant exceptions neither academic nor popular discussion has looked "upstream" (...) to the social arrangements that determine the health achievements of societies.

The remaining part of this discussion will be organised according to the previously presented criteria for sustainable development. To begin with, I will outline a preliminary list of *criteria for sustainable and responsible, individually targeted preventive medicine*. As previously mentioned, the list is inspired by the criteria made by economist Michael Jacobs, presented in chapter 4.2.2. Subsequently, each criterion will be outlined and its relation to the five papers of this thesis emphasised.

9.2 Criteria for sustainable and responsible preventive medicine

Compared with Jacobs' version, my list of criteria entails some changes, made to accommodate the particular topic of individually based preventive medical activities as practiced in Western countries. Primarily, I have moved Jacob's final concept – which he termed *Quality of life* – to the top of the list and renamed it. The concept thereby becomes the most fundamental criterion, and I call it *A balanced theoretical approach to preventive medicine*. Secondly, I emphasise that Jacob's principle of environmental precaution is applied in a broad sense. I thereby draw attention to our existential, social and cultural environment in addition to focusing on preserving and protecting the natural (physical) environment. Such a broad interpretation has also been used by other recent thinkers on the topic of sustainable development (Stefanovic 2000). The final point regarding the adaptations is that, for this particular purpose, I found it possible to combine two of Jacob's criteria. *Policy integration* and *Participation and Democracy* have therefore been combined into a single criterion which has been designated *Democratic goal-setting,*

participation and policy integration. I want to emphasise that the list itself, as well as its specifications, should be considered as a work-in-progress.[117]

These are the criteria I suggest for sustainable, responsible preventive medicine:

- *A balanced theoretical approach* to medical practice implies that knowledge about the human condition must build upon both the natural and the humanistic sciences.
- *Environmental precaution*, in the context of medicine, can be taken to mean that potential detrimental side-effects of medical activities must be systematically anticipated, supervised and minimised.
- *Equity* in medicine is a comprehensive issue, with major political implications. Here, I will only address the importance of keeping a sound balance between doctor-initiated, technological preventive activities, aiming at what may be called 'population care', and medical activities that are directed by the expressed problems, concerns or wishes of people seeking care or advice.
- *Democratic goal-setting, participation and policy integration* means that all relevant stakeholders should be involved in defining, coordinating and evaluating the overall vision, philosophy and strategies of preventive medicine. Preventive recommendations in particular areas need to be harmonised and prioritised in accordance with the overall vision, and the expected impact of new recommendations on clinical practice should be an integrated part of guideline development.
- *Planning for the future* is a topic that can be addressed from various angles, depending on context. Here, I take it to represent two issues which I see as important for the long-term planning of sustainable and responsible preventive medicine: first, we should remember that our priorities and actions ought to appear justifiable and reasonable, not only from the point of view of evidence-based medicine as it appears here and now but also from a more distant or even global perspective, or as regarded by the generations following us who are making medical reality today. In addition, I believe we should continuously consider to what extent the research questions we ask and the decisions we make as

[117] An earlier and less developed version of this list was published in the *Scandinavian Journal of Primary Health Care* in 2005 (Getz et al. 2005).

professionals are concordant with what rings true and is important to us as fellow human beings.

9.3 Balanced theoretical approach

A balanced theoretical approach to medical practice implies that knowledge about the human condition must be sought from both the natural sciences and the humanities. Biomedical measures are only part of what is relevant with regard to human health and disease. Responsible medical care must recognise, and should also make systematic aims to further conceptualise, the strong impact of social conditions and interpersonal relationships on health, on both the individual and the group level.

In the Nordic countries, the healthcare system can be conceptualised as a *societal* institution, mandated to help sick people and prevent human suffering. Implicit in this mandate is the power to exercise actions based on knowledge. As Reidun Førde has emphasised (see chapter 2.3.3), scientific medical knowledge informing medical practice must be 'true' in order to be ethically justifiable. By true, she – as I interpret her – means *correct, valid*, and also *adequate*. Although it can prove sufficient in many practical instances, medical knowledge derived from the presumption that a human being can be regarded as a biological clockwork (see Appendix 2) is *not true enough*, in this comprehensive sense. As Eric Cassell, Drew Leder, Ian McWhinney, George Engel, Anna Luise Kirkengen and many other thinkers and researchers have pointed out (see the theoretical introduction), the Cartesian rational model of the body-as-nature is not *humane*. Austrian philosopher Herbert Pietschmann formulates this in his essay *Merits and limits of applying the scientific method to human society* (Pietschmann 2001):

> Any health system has to take into account the great achievements of scientific rationality, otherwise it violates the right of human society for the best possible treatment of illnesses. On the other hand, if this health system restricts itself to the frame of scientific thinking (in other words to scientific rationality), it violates human dignity. Therefore we reach the conclusion, that a health system, which sets out to be of benefit for human beings in their totality has to find a synthesis (or at least a balance) of these seemingly contradictory poles.

The challenge of striking a balance between the 'rational and scientific' versus the 'hermeneutical and humanistic' approach, is a central topic of all five papers in this thesis and the core topic of Papers II and III.

9.3.1. The characteristics of humane medicine

Humane[118] refers to "what is fitting for a human being", or to "what is rightly to be expected of mankind at its best in the treatment of sentient beings; a humane enterprise or endeavour is one that is intended to prevent or relieve suffering" (Pijnenburg 2002). What does this mean in a medical context? On the one hand, humane medicine respects every patient as an autonomous and self-determining person. On the other, and at the same time, it respects man's fundamental dependency and contingency (Pijnenburg 2002). There may be few fixed universal criteria for what fits a human being; much depends on cultural perceptions of the good life and the good which human beings are striving for. But since medicine involves the science and art of helping people, one could expect that medical professionals would show considerable interest in finding out what is generally considered good for and by people, at least in the cultural context where they practice. Canadian professor of philosophy Charles Taylor (b. 1931), who is among the foremost thinkers on modernity (Taylor 1989 and 1991), has however observed that in the modern Western world, people very seldom reflect upon the question of *what it means to be a human being*. In a way this fundamental question is removed from the agenda of modernity.[119] Taylor observes that in the wake of the naturalistic philosophers, beginning with the Scientific Revolution, Descartes and the Enlightenment researchers (see Appendix 2), there appears to be a silence – Taylor calls it *inarticulation* – about our deepest moral and spiritual intuitions. In Taylor's mind, this inarticulation has come to threaten the achievements of modernity (Taylor 1989). In his work *The ethics of authenticity* (1991), he explicitly describes how inarticulation poses a particular great challenge to health care. Along similar lines as Heidegger and Jonas, Taylor believes that we stand before some fundamental choices in relation to how we will utilise technology. Will we adhere to Cartesian technological enframing aiming at *control* over nature, or will we aim for *authenticity*? Taylor speaks of "runaway extensions of technological reason" in modern health care and suggests (Taylor 1991:106):

[118] According to Merriam-Webster's dictionary (2005), the word humane means: marked by compassion, sympathy, or consideration for humans or animals.

[119] In The Norwegian context, I see professor of philosophy Arne-Johan Vetlesen as an eminent exception to this rule. I still remember the impact he made on the group at the 2002 Rosendal seminar when he listed what he saw as the basic premises of human life. He discerns *mortality, vulnerability, dependency, existential loneliness*, and *the precariousness of human relations,* as later presented in the book *Smerte* [Pain] (Vetlesen 2004). Vetlesen has also reflected on some implications of these premises for the medical encounter (Vetlesen 2001).

> Instead of seeing it [technology] purely in the context of an enterprise of ever-increasing control, of an ever-receding frontier of resistant nature, perhaps animated by a sense of power and freedom, we have to come to understand it as well in a moral frame of the ethic of practical benevolence. (...) But we have to place this benevolence in turn in the framework of a proper understanding of the human agency, not in relation to the disembodied ghost of disengaged reason, inhabiting an objectified machine. (...) Technology in the service of an ethic of benevolence towards real flesh and blood people.

At the 35th meeting of the *Society for Neuroscience* in Washington in November 2005, the Dalai Lama, renowned for his enthusiastic interest in science through 20 years of contact with prominent researchers around the world, addressed almost 14.000 participants in a keynote lecture.[120] His message was thought-provoking and obviously controversial to biomedical scientists:

> It is all too evident that our moral thinking simply has not been able to keep pace with such rapid progress in our acquisition of knowledge and power.
>
> It is no longer adequate to adopt the view that our responsibilities as a society is to simply further scientific knowledge and enhance technological power and that the choice of what to do with this knowledge and power should be left in the hands of the individuals.

How might it be possible for us, as a scientific community, to create a penetrating and engaging debate about what impact we will 'allow' technology to have on us – as individuals, as a profession, as a society? The freedom of basic research is one of the pillars of academic life and scientific endeavour (Jonas 1985: 90-108). Thus, the challenging cluster of *knowledge*, *power* and *responsibility* cannot be addressed from the question: should political or societal control secure the "right" type of knowledge production? And certainly, when applied to medicine, no ideology or government should direct medical research. So much should have been learned from the lessons of Auschwitz.[121] But if we, from where we stand today, follow in Taylor's footsteps, inspired by Arthur Frank's idea of ethics as a continuous and conscious way of being, one could begin, for instance, by examining the role of medical ethics, ethicists and ethical review boards and committees in modern health care.

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[120] Marc Kaufman: *Dalai Lama Gives Talk on Science.* Monk's D.C. Lecture Links Mind, Matter. The Washington post, Nov 13th 2005.

[121] Lifton R.J. *The Nazi Doctors: Medical Killing and the Psychiatry of Genocide.* New York: Basic books, 1986.

Personally, I could imagine ethical committees reminding and challenging medical researchers and practitioners to reflect more deeply on the true nature of human beings. What happens in today's reality is, however, that medical ethics is most often applied in a – paradoxically enough – technological and instrumental manner: much of its mandate appears to be limited to protocol-driven, superficial questions, such as how given information or consent letters should be written. I agree with researchers like Chorover (see chapter 4.1.5), who propose 'institutionalising' a more challenging ethical debate about what type of medical research is needed. And whether research activities currently exist that, despite permissions granted by ethical review boards, can be seen as threatening to dehumanise us. It would also be interesting to address more systematically how the medical research agenda interacts with society-at-large, both in an 'upstream' and 'downstream' manner.[122]

9.3.2 From 'evidence-based' to 'adequate' recommendations?

All papers in this thesis, and in particular Paper II, illustrate how the concept of evidence, as defined in the particular and demarcated context of evidence-based medicine (EBM) has become an indisputable 'good' in contemporary medicine; how it has attained the status of being almost synonymous with scientific truth concerning health and disease, and how it thereby renders other ways of 'knowing' less relevant and valid (see chapter 2.2.7). As previously outlined, EBM is notably silent on the values and judgments going into empirical analysis and research, from designing the study to interpreting the data and applying it to patient care. The term *evidence* suggests that something has evinced, come into being, 'come forth' by itself. The term conceals the fact that the knowledge termed evident is the result of scientific construction and, as such, a forth-bringing of a particular kind of knowledge about something. The term *evidence-based* suggests that the evidence, as such, speaks, guides, and decides what is best (Goldenberg 2005, Raine et al. 2005).[123] The existence of 'evidence' thereby appears to carry with it an imperative to intervene to change reality. As mentioned, philosopher Charles Taylor has for two decades puzzled over this enduring dominance – in language,

[122] By upstream, I mean the discourses informing the making of medical research projects. By downstream, I mean the way the medical research agenda comes to affect individuals, society and the healthcare system. At the 2004 Rosendal conference, one session was devoted to this kind of ethical analysis (conducted by Roger Strand and Yngvild Hannestad, researchers at the University of Bergen).

[123] Kernick (2005) notes how dichotomizing results of trials according to whether they are statistically significant or not can apparently be seen as producing yes-no responses to decision makers.

practices and institutions – of what he calls "naturalism", the view that humans are not only part of nature but should be understood according to the canons of the Scientific Revolution and the Enlightenment, which ultimately aim for control over nature (see Appendix 2). In an attempt to explain why this is so, Taylor observes that all human communities are defined, guided and structured by what he calls *hyper-goods* (or hyper-values). This also appears to be true in the realm of the human sciences. Taylor defines hyper-goods as "goods which not only are incomparably more important than others but provide the standpoint from which these must be weighed, judged, decided about" (Taylor 1989:63). He furthermore believes that the force of the natural science paradigm derives "from the underlying image of the self ... and the images of freedom, dignity and power which attach to it" (Taylor 1985, quoted in Gordon 1988). *There therefore appears to exist a mutual reinforcement between the naturalistic biomedical paradigm and the Western ideals of individualism and autonomy* (see also Gordon 1988).[124]

In a medicine aspiring to be sustainable and responsible, the epistemological limits of contemporary evidence based approaches, and questions of what kinds of evidence should inform current medical research and practice, should receive more attention than is currently the case (Malterud 2002; Goldenberg 2005). The reason is that even when medical evidence is technically *correct and just*, which may, in fact, not always be the case (as demonstrated in Papers I and V), one should still remain free to question whether it appears adequate to act upon the evidence. Evidence can in no way be regarded as 'given;' it must undergo the social processes of production, interpretation, evaluation, and application before it can be the foundation of any decision. To paraphrase the philosopher David Hume's teachings in *A treatise of human nature:* normative "ought" statements like guidelines cannot be derived from descriptive "is" statements like research evidence (Raine 2005).

[124] We thereby keep applying the same epistemology and methodology to the exploration of human beings, human health, and more recently, human experiences of meaning and value as we do to the exploration of nature. Take as an example the increasing interest for what is called 'evidence-based bioethics' (see Halpern SD. *Towards evidence based bioethics*. BMJ 2005;331:901-3). This trend has been analysed by US philosopher Maya Goldenberg (Goldenberg 2005). The impact of this *categorical mistake*, as the Norwegian philosopher Hans Skjervheim has termed it (Skjervheim 2002), under the influence of the latest hyper-value in medicine, which appears to be evidence, has been elicited by contemporary Norwegian psychologist Tor-Johan Ekeland in his critique entitled *Evidensbasert behandling: kvalitetssikring eller instrumentalistisk mistak* [Evidence-based treatment: quality assurance or instrumental mistake?] in 1999.

Instead of relying almost solely on the hyper-values of *objectivity* and *evidence* in the context of biomedical research, one could continue in the footsteps of Charles Taylor and consider whether medicine needs another hyper-value besides evidence, namely that of *adequacy*.[125] If medical research were, above all, judged by its level of adequacy, it would be validated differently from what it is now. The validating question underlying EBM of "is this a correct finding in human bodies?" would then be followed by other crucial questions: "Does this approach do justice to the nature of human beings?" Or: "Does this method account for the actual social context?" And: "Does this interpretation account for all relevant dimensions of meaning?" *The best account principle* is, according to Charles Taylor who elaborated the term, what should guide our description of reality and our ethical considerations. At this level, one may approach questions, such as whether it represents reasonable and adequate medical action to personally communicate existing evidence to a large majority of the individuals in one of the world's longest-living and healthiest-living populations that they are at high risk of ultimately dying from cardiovascular disease (Papers IV and V). In the context of adequacy-based medicine, it might also become easier to discuss whether it is good medicine to impose 'evidence of bad health' upon an elderly gentleman who feels he is in a state of good health and seeks out his doctor only because he needs a medical certificate to get his driver's licence renewed (Paper II).

9.3.3 From Cartesian dualism to the Lived body

It is no easy matter to challenge "the Cartesian position" in medicine. It is so firmly entrenched in our culture that it is difficult both for medical professionals and lay people to think beyond its horizon (see chapter 2.2.6 and Appendix 2). One may begin by considering terminology, the words directing our thoughts and our way of questioning human health and disease. As Heidegger and other thinkers have shown, in the ancient Greek world there was no dichotomy between the body and its intentions. Also, several thinkers believe that what we must do is re-invent a conceptual framework transcending 'the mind-body split' (Bracken and Thomas 2002). Among these scholars is medical doctor and philosopher Drew Leder who has worked with the phenomenological notion of *the*

[125] I am indebted to Anna Luise Kirkengen, who, on the basis of Charles Taylor's teachings, introduced the concepts *Adequacy* and *Best account principle* as potential tools for medicine at the 2005 Rosendal seminar. According to Merriam-Webster dictionary, adequate means "sufficient for a specific requirement; or lawfully and reasonably sufficient."

Lived body, as opposed to the *Cartesian material corpse*.[126] The concept of the Lived body implies that *the body of a living being has an essential structure of its own which cannot be captured by the language and concepts we use to describe and explain inanimate nature*. The Lived body is a perceiving, experiencing and 'intending' entity – bound up with and directed toward, an experienced world. It is a *being in relationship* to that which is other: other people, other things, an environment. Furthermore, the Lived body is our gateway to experiencing the world. Through our senses, our motility, and our desires, the world 'comes to be' by way of our bodies. As Leder (1998:124) formulates it: "To be human is to be the site of an intentionality which is materially determined and enacted."

Papers IV and V of this thesis, as well as Appendix 4, illustrate how current clinical guidelines build upon evidence about that human condition that is highly selective, with a strong bias towards decontextualised, biomedical measures. Even this demarcated approach is characterised by many simplifications. As a professional community, we have to start envisioning medicine – and a healthcare system – where biological and existential approaches are somehow interwoven in more complex patterns (Wade and Halligan 2004). Leder speaks of "mutually implicatory and involved in intricate 'logics' of exchange" (1998:125). To take an example: at the epistemological 'chiasma' where meaning meets matter, a clinical phenomenon, such as hypertension, cannot be addressed only as a question of circulatory dynamics. In parallel, it would always be addressed as a potential reflection of the person's social and existential *situatedness* and style of being-in-the world (see 2.1.4). The existential account should obviously not replace the biological account, but place it in a wider perspective. As Leder says: "To attend to the lived body is not to forsake the tools and learning that Cartesian medicine has provided. It is merely to refuse to grant this mechanical wisdom the status of ruling paradigm" (1998:127).

Once it is understood that disease has existential dimensions no less important than its physiology, or, formulated more decisively, that *physiology is enacted by experiential phenomena*, new methods of clinical evaluation and intervention become available to the clinician. The pa-

[126] In the German language, there is in fact one word to designate the living body, – Leib; and another word for the dead body, Körper.

tient's story would not only be interesting for its own sake, or as part of the process of creating trust and eliciting the patient's concerns and expectations to reach a common understanding of the biomedical condition and enhance the patient's concordance with the doctor's suggested treatment. The patient's narrative would provide genuine understanding of the social and existential preconditions of health and disease in this particular person (see chapter 2.1.4: *Situatedness, embodiment and health* and chapter 2.1.5: *The health benefits of a narrative*). Correspondingly, medical interventions would not be "bounded by the flesh only," meaning addressing human biology by technological approaches involving drugs and schematic lifestyle advice. Scientifically founded medical intervention might aim to alter the individual "body-world relation" and strive to reduce existential *dis-ease*.

As said above, a comprehensive approach departing from the notion of *the Lived Body*, appears to require development of a fundamentally new theory and terminology. Important innovation is already taking place in this field; this can be exemplified by the emerging concepts *allostasis and syndemiology* (see chapter 2.1.4). Acknowledgement of *complexity* as opposed to linear causality (see chapter 2.2.5) also appears promising as it allows anticipation that in clinical practice, small initial changes can have important end results that could hardly be accounted for by conventional, linear cause-and-effect models. If medical professionals began to emphasise the notions of Lived body, complexity and adequacy, exploration of an individual's *health resources* would also appear more essential than it does today (Malterud and Hollnagel 1998; Hollnagel and Malterud 2000; Malterud and Hollnagel 2004).

9.4 Environmental precaution: minimising adverse effects of medical activity

This component of sustainable development means that we have a responsibility to pay systematic attention to conceptualising, predicting and preventing adverse side effects, harm and undue medicalisation that can result from medical activity, on the level of individuals, the healthcare system, our physical environment and society-at-large. In the general theory of sustainable development, *the precautionary principle* states that lack of scientific proof of detrimental effects of current activities is no argument for postponing measures to discover, conceptualise and prevent them.

This approach has much in common with, and is indeed inspired by, the way Ivan Illich conceptualised 'iatrogenesis' in the 1970s (see chapter 2.3.4). All five papers in this thesis outline potential harm related to preventive medical activity, and together they cover a wide spectrum of effects. In the theoretical introductory part, I have mentioned some other concrete examples of harm that has resulted, or can be anticipated from, preventive medical activity. The types of harm can be classified as follows:

Concrete risks to the physical health and well-being of individuals. This may result from clinical uncertainty engendered by ambiguous or false positive test results in screening/prevention (systematic or opportunistic) activities in clinical practice. An option of further investigations and/or treatment interventions typically follows in the wake of such results, and these interventions may entail a potential for physical harm (Ewart 2000, Welch 2004). Documentation of this kind of harm, following in the wake of ambiguous findings by ultrasound screening, is the main topic of Paper I in this thesis, which demonstrates loss of wanted pregnancies caused by attempts to resolve technologically induced uncertainty.[127] Side effects of this kind have been known for many years, as has been highlighted in seminal papers by Black and Welch (1993) and Fisher and Welch (1999). Detrimental effects of cancer screening programmes are the focus of a new book written by Gilbert Welch, who is a US physician and professor in the field of community and family medicine (Welch 2004). He believes it is important to inform healthcare professionals and the general public about the 'downsides' of medical screening programmes. His aim is to educate people to enable them to protect their vulnerability in a healthcare system that is characterised by a strong *bias towards action*. The reason is that, in relation to medical

[127] The concerns expressed in Paper I have been validated in various ways after its publication. The fundamental – and thereby predictable - link between technological advancement and moral dilemmas in the context of prenatal medicine was recently confirmed by the previously mentioned study by Williams et al. (2005). The particular relation between the experience of false positive test results and profoundly distressing emotional experience among pregnant women has also been confirmed in a Swedish study on women's experiences of first trimester ultrasound screening (Georgsson Öhman et al., in press). In this study, 24 women who had received information about an increased risk for chromosomal deviations according to nuchal translucency screening, were interviewed during pregnancy and after birth. Twenty of these women had false positive tests, and for 16 the risk was higher than expected, considering their age. These women expressed major worry, and many said they chose to reject their pregnancy, to take "time out", while waiting for the results of fetal karyotyping. Two months after the birth, most of these women, however, seemed to have overcome the stress. Some of the women nevertheless expressed serious concerns in the interview as to whether it was ethically justifiable to offer a medical test like this on a routine basis.

screening and diagnostic testing, *more* is not necessarily *better* (Fisher and Welch 1999; Del Mar and Glasziou 2003).

Ecological and biological hazards. This, for instance, can be radiation exposure affecting investigated individuals directly as well as the population in general, due to increased background radiation resulting from medical activity (see chapter 2.3.4 with references). This particular topic is not a main focus of this thesis, but it belongs to a general discussion of sustainable, preventive medicine. In addition, the use of ultrasound in pregnancy can serve as a good example of activity in need of close surveillance due to a theoretical risk of biological hazard (Westin and Bakketeig 2003). Several authoritative bodies in the USA have recently called for responsible use of ultrasound during pregnancy, where it has been increasingly promoted as 'boutique fetal imaging' (Chervenak and McCulloch 2005).

Negative social and cultural impact of medicalisation of human life. This refers to the potential for negative and disempowering effects of medically related programmes and initiatives aiming at enhancing people's health and coping with life. The potential for unfavourable medicalisation of a given (in this case a statistically healthy and long-living) population is a core topic of Papers IV and V in this thesis. And it is not only *disease prevention* programmes that should be watched critically. New Zealand researchers Buetow and Docherty (2005) also warn that in relation to general *health promotion* activities, "there is an unmet need for evidence not only of effectiveness but also of the physical and cultural safety."

The previously outlined repressive and coercive forces in medicine which have been conceptualised and described by several scholars in terms of medicalisation, medical policing and disease mongering (see chapter 2.3.5) should be acknowledged at this point. These forces may come to the surface as incidental and unintended violations of individual patients' autonomy and integrity (as described in Paper II), but may also take the form of systematic projects designed by 'the medical-industrial complex', aiming to expand the number of consumers asking for, and patients perceived to be in need of, medical care 'for their own good.' The importance of reflecting upon the coercive potentials of preventive medicine was explicitly mentioned in the proceedings of the *Goals of medicine project* (Callahan 1996:16):

> The temptation to use medical knowledge and skills to manipulate or coerce whole classes of people or whole societies in the name of improved health, social well-being, or cost-control is likely to become increasingly potent, and enormously seductive, in the years ahead. (...) It is a development to be carefully watched and generally resisted.

I agree with Callahan and co-workers who see this as "a threat to the institution of medicine and to human liberty and dignity."

A negative psychological and existential impact of risk labelling on the level of the individual is a well-known concern in relation to preventive medicine and screening programmes, as exemplified by the writings of Illich, Skrabanek, Stewart-Brown and Farmer (1997), and many others. The importance of paying attention to the potential for inflicting psychological or existential harm as a result of implementing new, preventive technology in clinical practice is a topic of all papers in this thesis, and particularly Paper I. Previous findings of how false positive results from ultrasound screening in mid-pregnancy may have a dramatic emotional impact on the pregnant woman have recently been confirmed in a Swedish study on early ultrasound screening (Georgsson Öhman et al., in press). As previously outlined, Paper I contains an argument which extends even to the psycho-physiological interface between the expectant mother and the child-to-be. The hypothesis that medically induced distress might cause subtle harm to the unborn child appears even more plausible today than when Paper I was first submitted in 2001 (see chapter 2.3.4 with references).

Another type of harm that may accompany preventive medical activity is the focus of Paper III. This is the possibility that technologically oriented preventive medicine will distract the dialogue between patient and doctor from other issues that are important to the patient's health. As Welch puts it (2005:662):

> ...this downside of screening is not frequently discussed, and the evidence that it exists is anecdotal. But I believe it's real. The more time we spend prescribing, ordering, communicating results, and following-up abnormal findings, the less time there is to spend with the patient's concerns.

I will let this last quote serve as a bridge to the next topic, which is *equity*.

9.5 Equity: balancing the doctor's and the patient's agenda

I will focus only on one element of equity in this discussion, and that is the need to find a sound balance between the 'doctor's agenda' of clinical recommendations, based on EBM as we know it today, and the agenda which the individual patient brings to the clinical encounter in primary health care.[128]

The pressure from health policy initiatives on general practitioners to share responsibilities for what can be called *population approaches to health care* currently appears to be increasing, in not only the Nordic countries but also the UK, Australia, New Zealand and other areas where family medicine has a strong position (Buetow and Docherty 2005). With this responsibility follows increased emphasis on the implementation of EBM and preventive medical guidelines in the clinical encounter. The traditional lines between *public health* (the act of improving a population's health through collective action), *population health care* (preventive activities recommended by a third party for implementation in primary health care), and *traditional primary health care* (typically initiated by the patient coming to the doctor with an expressed concern or wish) are thereby becoming obscure. This can be seen as a central topic of all papers in this thesis. Evidently, general practitioners in other parts of the world appear to be pondering the same questions. For instance, from the perspective of general practice in New Zealand, Buetow and Docherty write (2005:397):

> ...reasoned debate on the policy of introducing preventative care and health promotion initiatives in clinical practice is overdue, not least in New Zealand, where clinicians within general practice appear to have been seduced by the lack of clarity in health policy into accepting this policy without question. They appear to disregard implications of the policy for redefining the nature and scope of their discipline (and of public health), including their own role as providers of personal care.

I personally believe that in order to preserve the dignity of our patients, the quality of medical care, and - as a logical consequence – people's trust in the medical profession, primary healthcare physicians should remain committed first to responding adequately to patients' expressions of experienced problems or wishes in terms of medical assistance. Only

[128] In the theoretical introduction to this thesis, I outlined the concept of patient-centred medicine (see chapter 2.2.6), which is based on the notion of 'agendas' and defines a patient's agenda in addition to (or rather in parallel with) the *doctor's agenda*. The theory of patient-centred medicine was developed before the introduction of EBM, and it did not specifically address the issue of evidence-based clinical recommendations in the way I do here.

thereafter does it appear reasonable to prioritise well-documented, cost-effective and safe preventive activities within the limits of available resources. It is fundamentally important to protect the clinical encounter from becoming instrumental to an extensive "checklist agenda" that is mainly defined and monitored[129] by a third party, and thereby becomes alienated from its main purpose and dehumanised in its nature. If this were to happen, patients would be alienated from their lives, bodies and needs. The same might also gradually happen to the doctors who exercise an alienating medical practice.

9.5.1 The 'carrying capacity' of the consultation

One approach to the discussion of a balance between agendas is considering what we might call "the carrying capacity"[130] of the consultation and the primary healthcare system. Such an analysis could begin with simple considerations of *the time available* for preventive interventions versus 'other' purposes in the consultation. This has already been outlined in Paper III. As presented there, a recent study (Yarnall et al. 2003) showed that in the US context, 7.4 hours of the working day of an average primary care physician would be needed to provide all services recommended by the US Preventive Services Task Force. The same research group subsequently calculated the time needed to provide recommended care to patients with *chronic diseases* (Östbye et al. 2005). It appeared that if guideline recommendations for 10 common chronic diseases were applied to a panel of 2500 primary care patients with an age-sex distribution and chronic disease prevalences similar to those of the general US population, the minimum physician time required to deliver high-quality care would exceed the total time currently available for patient care. These modelling studies are not directly transferable to the Nordic setting, but they indicate that dictums of authoritative guidelines can be grossly incompatible with clinical reality. Once this is documented, new light is shed on the important and well-documented fact that general practitioners show limited adherence to clinical guidelines. This phenomenon has been highlighted in Papers II-V and will also be touched upon in the next chapters.

[129] There may also be economic incentives connected to this monitoring, as will be outlined below.

[130] The notion of carrying capacity is well known from discussions related to economic growth and exploitation of natural resources. See, for instance, the seminal book by Meadows D et al. *The Limits to growth* (1972), which presents the works of the so-called Club of Rome, involving a group of MIT scientists who developed scenarios for the future. Limits to growth was among the works leading up to the interest for sustainable development and the Brundtland Report in 1987.

Research into communication in primary health care usually focuses on *what takes place* and more rarely investigates the aspects of clinical communications left unspoken. Preliminary research made by the Canadian research group conceptualising *patient-centred medicine* (Levenstein et al. 1986; McWhinney 1989) documented that doctors often fail to elicit the patient's actual reasons for consulting, or other worries that bother them. Time restraints may evidently contribute to this. Recent research has shown that emotional and social issues are the topics most likely to be underrepresented in the consultation. In a recent qualitative study involving 35 patients consulting 20 GPs, a UK research team systematically investigated issues that were important to the patient, but not elicited in the consultation. The findings indicated that, compared to the research interviews conducted after the consultation (Barry et al. 2000):

> in consultations patients seem only partially present, with only limited autonomy – that is to make requests but not suggest solutions. Outside consultations patients are more fully present: as socially and contextually situated, thinking, feeling people, with their own ideas on their medical condition (...) This suggests that in the consultation, the patient is most commonly construed as a purely "biomedical" entity.

The authors conclude that what they call "partial voicing" and facilitation of certain agendas at the expense of others may produce less effective consultations. The fact that unvoiced topics can have detrimental effects on the clinical outcome, either by way of negatively influencing adherence to prescribed treatments, or because they pave the way for misunderstandings, has also been documented in other settings (see references in Barry et al. 2000).

9.5.2 Patients and doctors as moral strangers?

In a paper titled *The doctor, his patient, and the computerized evidence-based guideline*, a British general practitioner reflected upon empirical studies which have showed that computerised guidelines for treatment of asthma and angina[131] are often ignored in clinical practice (Lipman 2004). It appeared that the GPs thought that the guidelines imposed an external, largely biomedical, agenda that tended to supersede the pa-

[131] These studies were 1) Eccles M et al. *Effect of computerised evidence based guidelines on management of asthma and angina in adults in primary care: cluster randomised controlled trial.* BMJ 2002;305, 941–944. 2) Rousseau N et al. *Practice based, longitudinal, qualitative interview study of computerised evidence based guidelines in primary care.* BMJ 2003; 326, 314–318.

tient's. The technical nature of the guidelines somehow disrupted the normal pattern and power balance in the GP consultations (see also the discussion of EBM in chapter 2.2.7). It can be seen as rather thought-provoking that even in relation to people having the diseases for which the guidelines have been developed, EBM may conflict with patients' needs and wishes. Lipman explains this in terms of a fundamental conflict between *care* and the values underlying *medical science*. With reference to the motto of the Royal College of General Practitioners, *Cum Scientia Caritas*, he writes (Lipman 2004:173):

> The implementation of a research agenda promoted by guideline committees and their assorted apparatus of quality frameworks, guidelines and computerized flow charts elevates *Scientia* into the prime purpose of clinical practice while removing control of it from clinicians. In such circumstances, *Caritas* is relegated to second place and may be seen as conflicting with *Scientia*. This is not only uncomfortable but positively harmful. It undermines GPs' professional status and their confidence in making their own judgements, and subverts their well-evolved culture of holistic practice focused on individuals and their families.

From a corresponding perspective, New Zealand general practice researcher Stephen Buetow also addresses the term *care* (Buetow 2005). He emphasises that, by definition, *to care for someone* is to engage in "a reciprocal relationship and intersubjective experience that the patient or clinician cannot define alone. Clinicians care with, rather than for, patients, and both benefit from care as a process and outcome." The importance of a reciprocal conceptualisation of care in contemporary medical reality is also reflected in a paper by two British general practitioners focusing particularly on the large group of patients with multiple problems and diagnoses (Heath and Sweeney 2005):

> As general practitioners focus increasingly on the management of people with multiple and compounding conditions, the balance of technical with compassionate care must be continuously negotiated so that it makes sense in the context of the patient's life story and acknowledges the full diversity of their health and social problems. In such a situation, the values and priorities of the individual patient must always be allowed to trump the dictates of medical science and evidence based guidelines. The ever present, malevolent potential of illness to destroy an individual's personhood can never be forgotten. Although biomedical interventions may become more sophisticated, and service delivery more slick, the responsibility of the general practitioner to acknowledge and, where possible, relieve suffering endures and can never be abrogated.

To sum up, it can be noted that the moral basis of what can be called a

utilitarian approach (implying that what is ethical, is what is believed to increase overall health or well-being in a group or society, something I see as congruent with the EBM approach), is, however, qualitatively different from *ethics of care*, implying that what is ethical is to respond to the needs of the unique individual. Both approaches are indispensable in the healthcare system. However, as discussed in the previous section, it is not self-evident that they fit equally well with the ethos of the consultation in primary health care (Summerskill and Pope 2002; Heath 2004). All papers in this thesis, and in particular Papers II and III, conceptualise how implementation of EBM may impose *an alien moral framework* in the clinical encounter. Buetow and Docherty (2005) are, as a consequence of this, concerned about what they call a "weakening of personal care in response to depersonalized population health agendas" and warn that patients and doctors may become 'moral strangers.' This could reduce patients' ability to access care that they can trust to be the best care for them in their situation. The same authors conclude (2005:402):

> We acknowledge a need for collaboration and coordination between general practice and public health. (...) However, population health care in general practice is appropriate only when this care is known to be safe and effective, and does not compromise personal care.

It should be noted that several of the arguments for providing *time, space and status to mutuality and genuine dialogue in the clinical encounter*[132] have been formulated in relation to implementation of clinical guidelines for secondary prevention and control of symptomatic disease. To what extent all these arguments are valid for primary preventive guidelines is open to debate. The relevance of finding this out, however, is great, as economic incentives are increasingly being used to direct clinicians' attention and actions towards monitoring and documenting their patients' biomedical health status on a regular basis (Boyd et al. 2005). Such an incentive system was, for instance, introduced in British general practice in 2004 (Roland 2004). When this idea was launched, it was described as "an initiative to improve the quality of primary care that is

[132] I would like to direct Norwegian readers to an interesting paper that addresses this topic from a broad perspective: *Dialogene som forvitrer. Et kritisk blikk på klinikkens utvikling*, by Ole Berg and Charlotte Haug (1997). Quote (translation by LG): "Medicine is becoming increasingly specialised and depersonalised. It would represent an irony of fate if medicine itself should contribute to processes that create the very problems it is supposed to reduce. Medicine should rather be characterised by a calling to strengthen the personalising processes – the genuine dialogues. (...) Industrialisation of medicine does not only come from outside (...) it also comes from inside: medicine shows tendencies to alienate itself and its representatives…"

the boldest such proposal attempted anywhere in the world" (Shekelle 2003). Opinions were, and still are, divided as to whether the overall quality of British primary health care will improve, and to what extent clinical practice will be informed by evidence, as opposed to becoming frustrated or coerced by it. Most observers, including those in favour of the system as such, appear to share the view that primary care is now likely to become more biomedically oriented, less holistic, and perhaps also more elitist – in the sense that patients who do not fit with the targets defined by the computerised monitoring system might feel less welcome in the doctor's office (Shekelle 2003, Roland 2004). The intensity of the reactions to this possibility, however, varies, as can be seen from the following two quotes:

> Will patients no longer be persons to the general practitioner but rather a series of performance targets to be met? This is a very real possibility, but I do not buy into the argument that improvement in one area of care must come at the expense of another (Shekelle 2003).

> They [doctors] will cease to be personal doctors and become instead disease managers. This is the ultimate expression of Ivan Illich's (1976) nightmare scenario. The management of health is becoming an industry in which individuals are seen only as members of groups with defined diseases. They will receive standardized interventions 'for their own good', and dissent will be seen as a threat to the doctor's earning and the Government's statistics, rather as a basic human right (Lipman 2004).

One final remark may be relevant here, as it links the notion of equity to the next element of sustainability, which is democratic goal-setting and policy integration. David Callahan and co-workers believe (1996;16):

> A medicine that knows no boundaries, that lacks its own compass, that is supine before the market, that forgets human finitude, cannot be an equitable medicine. It will follow money and power.

Thereby, one prerequisite for equitable medicine is that we make clear – to ourselves and to society – *the overall vision, mission, values and strategies of individually targeted preventive medicine.*

9.6 Democratic goal-setting, participation and policy integration

Democratic goal-setting and participation means that all relevant stakeholders – medical generalists, specialists, researchers and thinkers in other academic fields, health administrators, and also lay people – should be involved in defining, coordinating and evaluating the overall vision,

philosophy and strategies of preventive medicine. Policy integration implies that preventive recommendations in different areas need to be harmonised and prioritised in accordance with the overall vision. The expected overall impact of new recommendations on clinical practice should be estimated before guidelines are issued. In addition, assessment of the professional integrity of guideline authors is crucial.

9.6.1 Before choosing health, choose your philosophy

In a recent debate paper in *The Lancet*, titled *Choosing health? First choose your philosophy*, public health experts McKee and Raine (2004) called for an explicit and coherent philosophical foundation for the planning of programmes aiming to enhance the overall health of a population. They say:

> The first decision to make when developing a public-health strategy must be to decide the philosophical basis on which it is to stand.

I believe this was a timely and important reminder. Public health[133] initiatives often entail ethical challenges and dilemmas, such as how to prioritise scarce resources, and to what extent one has a right to approach individuals with a message that they should change the way they live their lives. It is quite evident that moral questions in these domains extend beyond traditional bioethics and require their own form of ethical analysis (Callahan and Jennings 2002, Beaglehole et al. 2004).[134] Health promotion and disease prevention programmes are clearly value-laden activities, and it is important to reflect upon the nature of the moral framework(s) underpinning medical activity of this kind. As mentioned in the opening part of this thesis, it can therefore be argued that *policy makers planning public health and population care activities need knowledge of philosophical theory, just as they must be familiar with epidemiological methods* (Roberts and Reich 2002).

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[133] The definition of public health has changed as the field has evolved. I will not discuss this here. I will however refer a recent definition suggested by Beaglehole et al. (2005): "Collective action for sustained population-wide health improvement." The disciplinary basis of public health can be narrow – mainly the medical sciences -- or broad and inclusive, bringing together a wide range of disciplines, including the political and social sciences.

[134] We have argued elsewhere (Getz et al. SJPHC 2005) that the four classical ethical principles can in fact be seen as challenged by the nature of the preventive medical paradigm: Preventive medicine approaches people who do not feel diseased and are not necessarily asking for help; the basis for *autonomy* may thereby be challenged. Furthermore, it applies measures that are derived from group-based knowledge and may have limited validity for the particular individual. This obscures the issues of *benefit* and *harm*. Finally, it focuses on highly selected biological variables that are often mediators rather than the true causes of ill health and health inequalities. This may challenge the principle of *justice* (interpreted in terms of justice-as-fairness).

9.6.2 Defining visions, goals and means for preventive initiatives

Prevention of CVD in the population-at-large is an activity that should have clearly defined goals and strategies. In practice, however, these are hotly debated topics; general practitioners, cardiologists, epidemiologists, pharmaceutical companies and other stakeholders present diverse and partly conflicting views of what should be considered a rational and reasonable approach (for various arguments, see Meland, Ellekjær et al. 2000; Law et al. 2004; Makover and Ebrahim 2005; or Jackson et al. 2005). In fact, if considering the matter from a philosophical viewpoint, it turns out that more than one strategy can be ethically defendable (Roberts and Reich 2002). To illustrate this, I will present somewhat simplified versions of two different approaches to CVD prevention in clinical practice.[135]

Approach 1: To reduce the total burden of CVD events in the population.

The aim here is to produce "the most gain for society," as measured, for instance, in disability-adjusted life years (DALYs) or quality-adjusted life-years (QALYs). This can be seen as a *utilitarian* approach. In practise, it implies reducing the risk level widely throughout the population, since most disease events will happen among people with a relatively unremarkable risk profile (because this group is so big). To reach such a target, it appears rational at first glance to systematically implement disease-preventive guidelines with a low threshold for intervention, such as the 2003 European Guidelines on CVD Prevention (given that implementation of these guidelines is effective in non-selected populations, which is not yet proven). Individual evaluation, counselling and monitoring according to such guidelines are, however, resource-consuming activities. Realising this, authoritative researchers have suggested that everyone aged 55 or older should take one 'Polypill' a day (outlined in Appendix 4, year 2003 on the timeline). This idea means to formulate a 'magic bullet' balancing anticipated[136] therapeutic effects against predictable adverse events, in a fashion calculated to keep the need for personal medical surveillance to a minimum. In relation to the use of lipid-lowering medication, this has been called a "fire and forget" approach (see Appendix 4). One might consider this to be some kind of a

[135] I do not consider public health *mass strategies* here, such as easy access to healthy food and a physical environment facilitating out-door activities.

[136] It has – on the basis of purely theoretical calculations – been anticipated that the *Polypill* could reduce the number of CVD events by 70-80%. Its effectiveness, however, has not yet been tested in clinical trials.

mass strategy, but implemented on the level of the individual. In a utilitarian framework such as this, it is not an ethical imperative to pay more attention to individuals at higher risk than the average or to young individuals. This is because the number of disease events that would occur, and might in part be prevented, among these groups would contribute relatively little to the total disease burden.

Approach 2: To try to avert premature death and disability among individuals going to the doctor and turning out to be at high risk for CVD.[137] These are first and foremost people who have already suffered a disease event or people seeking medical counselling due to CVD in their family or because of other concerns. Here, the motive is to help individuals asking for help to increase their chance of implementing what Rawls might have called their *life plans* (Roberts and Reich 2002). In this moral framework, one would not be concerned much about cardiovascular deaths occurring at a relatively ripe age (one might even argue that death from CVD might be preferable to death from a competing cause). On a macro level, the 'life plan approach' might not reduce the numerical burden of CVD deaths very much. This strategy might nevertheless be considered justifiable and coherent with Rawls' idea of "justice as fairness" (Roberts and Reich 2002).

In clinical reality, the line between the two approaches could hardly be very clear. It should also not be necessary to make a definite choice between these two alternatives. But for a discussion of preventive medicine to be creative and respectful, participants need to know that planning of preventive medicine does in fact involve philosophical deliberations and choices (McKee and Raine 2004).

Before closing this section on the importance of defining the moral foundations, goals and means of preventive medicine, I will highlight one final dimension of the debate about preventive medicine and population health initiatives: the question of *who is responsible for people's health*. What efforts are to be reasonably expected from society and what from the individual (McKee and Raine 2004)? I will not go far into this debated topic, but it is relevant to note that a recent Norwegian study of

[137] This argument presupposes that the screening tool (e.g. a CVD risk calculator) classifies a "reasonable" proportion of the population as at high risk, as opposed to the current version of the SCORE system (as discussed in Papers IV and V).

historical trends in political steering documents found an increasing emphasis on the individual's personal responsibility for making healthy life choices (Stenvoll et al. 2005).

Reflected against the background of the history of science, the increasing emphasis on the individual's personal responsibility for making healthy life choices can be interpreted as representing a scientific reinstitution of the concept of sin – no longer in the domain of the church, but in the medical context. As Deborah Gordon (1988:40) has noted, "Biomedicine has both created and stepped in to fill the apparent moral vacuum, replacing moral idioms with medical ones." Interestingly enough, the "breaking away of disease from the metaphysics of evil to which it had been related for centuries" (Foucault 1975; 198) was a core idea behind the progress that "the Enlightenment thinkers aimed at when devoting themselves to disengaging nature from its previous metaphysical and spiritual connections" (Gordon 1988; 24, see also Appendix 2 in this thesis). By defining *the body as the domain of science and the soul as the domain of religion*, disease was in the period of Enlightenment redefined to become a natural mechanism, and no longer a divine punishment for committed sins. Current implementation of scientific evidence, although presented to the public as free from morality and grounded in pure rationality and objectivity, is accompanied by a definite appeal to change personal "misbehaviour" in the sense of non-healthy living. In preventive medicine, one does not speak about the "sinful" person; the individual is encouraged to manage the "risky" self (Ogden 1995). In modernity's context of naturalism and individualism, we should acknowledge that preventive medicine can thereby come to assume the character of "normativity in scientific disguise" (see chapter 2.3.5).

Medical ethicist Richard Zaner (2003) has noted: "Medicine is one of the major remaining sources of taken-for-granted social authority in our times." Norwegian professor of social medicine Per Fugelli has, along with other previously mentioned scholars, expressed concerns that medicine is developing into *social authority which promotes moral blaming and coercion of people in the name of goodness and individual freedom* (Fugelli 2003 and 2006).

In his most recent works, Fugelli warns against medical equivalents to the "Zero Vision." In an attempt to counteract abuse of medical power,

he recently formulated a 'wish list' regarding values and strategies that he would like to see informing preventive medicine in the future (Fugelli 2003 and 2006). Fugelli wants to remould "the mind-shaping narrative power of public health education", and he proposes that the professional emphasis in preventive medicine should move:

- from *omnipotence* to *moderation*,
- from a focus on *life style* to a focus on *living conditions*,
- from *risk* to the *bright sides* of life (from pathogenesis to salutogenesis),
- from a *statistical clone* to a *holy individual*,[138] and finally
- the *public health messenger's style of communication* should change from what Fugelli sees as 'authoritarian truth mongering' to transparency, respectfulness, and acknowledgement of doubt in the face of uncertainty.[139]

9.6.3 Evidence-based guidelines versus reality-based 'mindlines'

In recent years, there has been considerable health service research on why medical evidence is not being more easily accommodated into practice, and how the perceived "barriers to implementation" can be reduced (see, for instance, Grol and Grimshaw 2003). As previously mentioned in this thesis and Papers II-V, the reasons for poor compliance with guidelines in clinical practice appear multifaceted and complex when contemplating the details (see, for instance, refs. 37-40 in Paper IV). From a meta-perspective, however, UK general practitioner David Kernick (2005) believes that these phenomena can be summed up in "*the fact that the evidence-based product may not be relevant to those at whom it is directed*." To explain what he means, Kernick describes an ever more solid consolidation of "two cultures"[140] in the contemporary British health service: the academic/researcher culture, on

[138] Here, Fugelli does not speak about individual responsibility for health, but about paying attention to each person's individuality and social situatedness, as opposed to treating him or her exclusively as a representative of a group on the basis of EBM.

[139] When choosing these provocative words, Fugelli is in good accordance with the founding father of EBM David Sackett who recently described the ethos of preventive medicine as arrogant; meaning aggressively assertive, presumptuous and overbearing (Sackett 2002).

[140] In a famous 1959 lecture in Cambridge and a subsequent book, physicist and writer Charles Percy Snow (1905-80) conceptualised a tension between the *two cultures of the sciences and the humanities*. Magne Nylenna has presented this topic to Norwegian readers (2000). According to Kernick, Snow saw a struggle of modernity that we can find 50 years later in health care as two groups struggling to "redefine the modern"; the health service academic/researcher and the clinician/practitioner (Kernick 2005).

one side, and the clinician/practitioner culture, on the other.[141] Kernick proposes that emphasis should shift from "bridging the gap" and "managing the interface" (which involves increased efforts to find ways to implement existing evidence in practice organizations) to undertaking a *fundamental reappraisal of the nature of the knowledge that is being produced by the healthservice academic community*. Kernick wants academic knowledge to become more coherent with "the realities of health services delivery."

In contrast to the way he describes the 'academic/researcher community' (see quote in chapter 2.2.2), Kernick conceptualises the 'clinician/practitioner community' in terms of *an eco-system of co-evolving elements* where one might regard "people coming together to make sense of their world within a framework that is largely socially constructed." Decision making in such healthcare communities is characterised by multiple goals and ambiguous and competing objectives, as well as uncertain relationships between cause and effect (see the section on complexity theory in chapter 2.2.5 in this thesis). Kernick states that "the bulk of our [GPs'] activity is to establish and modify relationships rather than seeking an endless series of goals." This description evokes sociologist Martin Lipsky's renowned theory of *Street level bureaucrats* (1980). There, Lipsky describes how practitioners in the front line of public service constantly strive to modify their roles and organizational expectations to reduce the gap between available possibilities and system objectives. With reference to Lipsky's theory, Kernick maintains that such strategies, which involve *a continuous negotiation between expectations and reality*, are absolutely essential to the long-time survival of the healthcare system. In order to fulfil professional expectations, the practicing clinician should thereby be encouraged to develop not only an evidence-based but also an intuitive grasp of reality. This grasp should be based on a deep understanding of the tasks at hand and *ability to take in complex situations and produce a vision of what is realistic to achieve* (Greenhalgh 2002; Kernick 2005). This understanding will be based upon experience with similar cases, underpinned by professional *reflection in action* (Schön 1983; Schön 1987; see chapters 4.1.2 and 7.1.3 in this thesis). In practice, such understanding is often developed in the presence of a collegial tutor or supervisor, i.e., within *a master-apprentice relationship*.

[141] Kernick's view that current biomedical research on medical interventions operates "on the flat of the exponential curve" and thereby yields marginal returns in terms of improved healthcare delivery, despite huge investments, was outlined in Chapter 2.2.2.

An in-depth ethnographic study from 2004 highlights how experienced clinicians in two highly regarded English general practices derive their individual and collective healthcare decisions (Gabbay and LeMay 2004). The researchers reported that "the individual practitioners did not go through the steps that are traditionally associated with the linear-rational model of evidence based health care – not once in the whole time we were observing them." Instead, the GPs relied on what the investigators termed "*mindlines*", which the researchers defined as *collectively reinforced, internalised, tacit guidelines*. The mindlines were partly informed by a brief reading of original research and guidelines outside practice hours, but mainly by the doctors' own experience and that of their colleagues, their interactions with each other and with opinion leaders, patients, and pharmaceutical representatives, and other sources of largely tacit knowledge. Mediated by organisational demands and constraints, mindlines were interactively negotiated with a variety of key actors, often through a range of informal interactions in fluid "communities of practice," resulting in socially constructed "knowledge in practice" (Gabbay and leMay 2004).

These findings have fundamental relevance to the planning of knowledge implementation and quality development in primary health care. Instead of defining the challenge as a problem of "poor concordance" and "clinical inertia" among clinicians, which are highly normative characteristics, it would be wise to acknowledge and respect the intricate processes of collective "sense making" by which knowledge, both explicit and tacit, is negotiated, constructed, and internalised in everyday clinical reality (Greenhalgh and Hurwitz 1998; Kernick 2005; Greenhalgh 2002).

In 1998, UK general practice researchers Greenhalgh and Hurwitz defined three aspects of what Kernick (2005) has termed "interface zones between evidence-based health care and the real world" which they believe need further scrutiny. I will highlight these areas, as they fit very well with the research and reflections I have presented in this thesis:

- Research trials are planned, funded, undertaken and disseminated within a historical, political, economical and cultural context.[142]
- The current tendency to overlook the difference between *efficacy*

[142] Comment by LG: Solid documentation of this can be found in the previously mentioned multi-disciplinary research paper (Krieger et al. 2005), which analyses the development of research, promotion and practice in relation to hormone replacement therapy.

and *effectiveness*[143] ignores the socio-cultural aspects of professional behaviour, organizational change and intervention delivery.
– The clinical encounter is an interpretative and creative act going beyond objective, scientific enquiry and must be separately studied by appropriate techniques.

It is obviously a challenge to change health service research traditions. But in recent years, there has in fact been an increasing emphasis on collaboration between researchers and the users of research results, as well as on involving patients at all levels of healthcare decision making. Against this background, programmes, such as 'action research' and 'knowledge utilization', have been launched. An overarching framework for involvement of relevant stakeholders in the development of new knowledge, termed *dialogical research*, has also been suggested (Schrijvers 1991).[144] According to Kernick (2005), this model portrays *research as a dialogue rather than an expert activity* and implies that all parties should be invited to contribute ideas and concepts to the research process in a respectful atmosphere.

9.6.4 Some notes on the process of guideline development

Despite wide recognition of the need for methodological rigour in the development of clinical guidelines, there is ample evidence that current approaches often lack sufficient quality and transparency (Shekelle et al. 1999; Hasenfeld and Shekelle 2003; Raine et al. 2005). As outlined in Papers IV and V, the 2003 European Guidelines on CVD Prevention in clinical practice evoke fundamental scientific and ethical questions, regarding both the quality of the biomedical evidence on which the risk scoring system is based, and the process of guideline development. The question of how to make clinical guidelines is, as such, not a central topic of this thesis. I will nevertheless sum up some points I have come to see as particularly relevant in the context of sustainable and responsible preventive medicine:

[143] Comment by LG: British pioneer clinical epidemiologist Archie Cochrane defined the concepts of efficacy and effectiveness. Efficacy is the extent to which an intervention does more good than harm under ideal circumstances: "Can it work?", usually referring to the context of clinical trials. Effectiveness assesses the extent to which the intervention does more good than harm when provided under usual circumstances: "Does it work in practice?", usually referring to unselected populations (Haynes 1999).

[144] Kernick's paper (2005) contains relevant references to action research and knowledge utilisation in clinical practice. The original reference by Schrijvers (which I have not read) is: Schrijvers J. *Dialectics of dialogical ideal age: studying down, studying sideways and studying up*. In L. Rencel & P. Pells (eds.) *Constructing Knowledge*. London: Sage, 1991.

– *The fundamental aims and philosophical approach(es) to the medical problem(s) in question* should be stated as explicitly as possible in the guidelines (as outlined in chapter 9.6.1). It should, for instance, be clear to what extent the recommendations aim for clinical effectiveness, cost effectiveness and equity.

– *The scientific knowledge and evidence, on which the guidelines are built*, should be comprehensive. As previously outlined (see chapter 9.3.2), it is neither rational nor reasonable to base clinical guidelines only on medical evidence, as currently defined by EBM (see also Holmen, Hetlevik et al. 1999; Raine et al. 2004).

– *The role of value judgements and group consensus* should be outlined in the guidelines. Specific methods have been developed for transparently incorporating group judgements in the preparation of clinical guidelines (Raine et al. 2005).

– *Participants in guideline development should be multidisciplinary*. It has been shown that when presented with the same evidence, a single speciality group is likely to reach different conclusions than a multidisciplinary group; the speciality group tends to be biased in favour of performing procedures in which it has vested interests (Shekelle 1999; Raine 2005; Krieger et al. 2005). All stakeholders whose activities or interests will be directly affected by the recommendations should therefore be involved from the beginning in the preparation of guidelines.

– *The question of efficacy versus effectiveness* must be carefully considered, (the terms are defined in footnote 143). Almost all clinical trials have until now assessed efficacy in the context of randomised clinical trials. Such trials have typically recruited patients who are carefully selected and diagnosed, lack other serious illnesses, are likely to follow and respond to the treatments of interest, and will be monitored with special interest and attention by the staff in accordance with a well-defined protocol (Haynes 1999).

A wealth of evidence from randomised controlled trials suggests that intensive management of hypertension, diabetes, dyslipidemias and other chronic conditions is, on average, beneficial to broad groups of patients in terms of disease outcomes (many of these trials are listed in Appendix

4). Until quite recently, most of the data have, however, been gathered in studies limited to single, clinical interventions (O'Connor 2005). The *effectiveness* of such interventions in non-selected populations in the community obviously depends on efficacy. Nevertheless, there is a whole range of additional factors influencing effectiveness, such as selection of patients, diagnostic accuracy, provider concordance, patient adherence, and locally available resources (Swensen 2000). With reference to the previously mentioned *precautionary principle*, it is important to acknowledge that potential harm is related to the implementation of efficacy-based guidelines in unselected populations. This will be illustrated with an example in the following paragraph about modelling studies.

'Implementation modelling studies' of guidelines should be mandatory before clinical guidelines are issued. Once an authoritative guideline is disseminated, it sets the standard for accepted health policy in its area. Adherence to guidelines is often used as a quality indicator and may even be linked to incentive payments (Boyd et al. 2005). Guidelines have important resource and equity implications; they stipulate what health resources should be allocated to which patients. They also have important implications for the distribution of health service resources among different specialities. Papers IV and V highlight the relevance of performing estimates of the implications of implementing guidelines, in terms of both the size of the target population and the accompanying workload. British GP and health economist Tom Marshall, who has conducted mathematical modelling studies of guidelines (e.g., Marshall and Rouse 2002), recently wrote (Marshall 2005):

> If guidelines are not to become simply marketing tools by which specialists try to increase the slice of health service resources allocated to their particular speciality, they must justify the resource implications in relation to the benefits they generate.

Marshall (2005) emphasises that analyses of anticipated effectiveness and workload implications are neither complex nor expensive to do. Still, to date, very few guideline committees have undertaken such analyses before issuing their recommendations. The 2003 European guidelines that are the focus of Papers IV and V are just one example of this. After the publication of Papers IV and V, another Norwegian study modelled the potential consequences of implementing the SCORE guidelines, based on data from the Tromsø population study. It documents that

implementation of the 2003 guidelines might lead to a doubling of the number of patients on cardiovascular medication for primary prevention, compared with the current status (Hartz et al. 2005).

Another type of modelling study that should be undertaken addresses the *aggregated effect of applying different clinical guidelines to patients with multiple medical problems* (Wright et al. 2003). An example of such a study was recently published in the *Journal of the American Medical Association*. It addressed the applicability of clinical practice guidelines in the care of a hypothetical older woman with several chronic diseases.[145] It turned out that most of the guidelines applying to her conditions did not modify or discuss the relevance of their recommendations for older patients with multiple co-morbidities. Most guidelines also did not comment on short- and long-term goals and the quality of the underlying scientific evidence or provide guidance for incorporating patient preferences into the treatment plans. If the relevant guidelines were followed, the hypothetical patient would be prescribed 12 medications, dosed three to five times a day and, in addition, a complicated non-pharmacological regimen. It was apparent to the investigators that medical errors, as well as adverse interactions between drugs and diseases, could easily happen. The resulting complex treatment regimen was also deemed likely to disrupt daily routines, impair social activities, and invite non-adherence. The authors' conclusion was that concordance with current guidelines in caring for an older person with several co-morbidities may have undesirable effects (see also Hetlevik 2005).

As noted in Paper V, the US Framingham study tended to overestimate risk in the European context, and this was one of the motivating factors behind the SCORE project. Now it turns out that the SCORE chart for high risk regions (including Norway) also overestimates risk. As outlined in Paper V, the SCORE-high chart appears to overestimate risk in the Norwegian population to a considerable extent. An even more recent study indicates that the same holds in Germany, and that the SCORE system overestimates risk to an even higher degree than the Framingham risk equation does (Neuhauser et al. 2005). Consequently, before issuing authoritative guidelines, *cardiovascular risk scoring systems should be*

[145] The patient had chronic obstructive lung disease, type 2 diabetes, osteoporosis and osteoarthritis; this combination of diseases is well imaginable in a women of her age. In the USA, it is estimated that half of the population aged 65 years or older has three or more chronic diseases (Boyd et al. 2005).

tested against epidemiological data gathered in the population where they are intended for use (Reynolds et al 2004, see ref. 13 in Paper V).

The final point I want to make regarding the development of clinical guidelines is that there should also be *transparency regarding competing interests among guideline authors/committees*. It is a well-established fact that the pharmaceutical industry's influence on medical practice has widely become too pervasive (see, for instance, Smith 2005 as well as several references in Appendix 4). Competing interests have been shown to introduce significant risk of bias in medical publishing. This made most leading medical journals introduce a competing interest statement for authors in the 1990s. In 2002, US internist Bob Goodman, who is the founder of a campaign for independent prescribing called No Free Lunch (www.nofreelunch.org), explained why it is particularly important that clinical practice guidelines are written by independent authors:

> Any influence of a drug company on an individual author [of a clinical guideline] is multiplied thousands of times. Worse, there's a subjective element to the recommendations in clinical guidelines that makes them particularly vulnerable to bias.[146]

In relation to compilation of clinical guidelines, the tradition of disclosing competing interests still appears to be very young (Papanikolaou et al. 2001, Choudhry et al. 2002, Smith 2005). For example, I found no statement about authors' and contributing experts' competing interests in the 2003 European Guidelines for CVD Prevention in Clinical Practice.[147] A study recently published in Nature (Taylor and Giles 2005) showed that about a third of authors who had recently written practice guidelines concerning drug use in the USA had ties to the pharmaceutical industry. It also showed that about 70% of guideline writing panels were affected. Furthermore, it also appeared that doctors quite often did not disclose drug industry connections, even when the guideline commitment or a scientific journal required it. I believe that a formal routine should be built into the process of guideline development compelling authors to declare, qualitatively as well as quantitatively (Smith 2005), any competing interests. A declaration of the contributors' competing interests should also be included in the written product.

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[146] This quote is taken from the News section of the *BMJ*: Tonks A. *Authors of guidelines have strong links with the drugs industry*. *BMJ* 2002;324:383 is accessible at www.bmj.com.

[147] I refer to the complete version of the guidelines: DeBacker G et al. Eur J Cardiovasc Prev Rehabil. 2003 Aug;10(4):S1-S78.

9.7 Planning for the future: closing remarks

According to my list, planning for the future is the final prerequisite for sustainable and responsible preventive medicine. The topic of futurity can obviously be defined very broadly. This entire thesis may, in fact, be regarded as an entry in the debate on medicine's future. It therefore feels appropriate to conclude the arguments I have already started, rather than introduce new and different perspectives that could also fit under this heading.

At the heart of medicine, in general, and primary health care, in particular, rests "the central, enduring responsibility of doctors in any society – the recognition and relief of suffering" (Heath and Sweeney 2005). In the hope of continuing to be satisfied and proud of my work as a medical doctor in the future, I have felt compelled to make this personal contribution to keeping medicine 'on the right track', with the hope that medical activity, in general, and preventive medicine, in particular, will be regarded as reasonable and justifiable, not only from the narrow perspective of evidence-based medicine here-and-now but also from a viewpoint of *geography* ("think globally, act locally") or *chronology* (how will my grandchildren describe the medical generation I belong to?). I therefore think we as medical doctors should strive to develop what has been called our human *moral imagination* (Benatar 2005 ii). This involves more human introspection and, at the same time, a more global orientation (Heath 2005).

Let us begin with the introspective part, as I believe it leads us to the global part. In the chapter *Man as standing- reserve?* which ended the theoretical introduction (Chapter 4.3), I asked whether the increasing international focus on dissatisfaction and so-called 'burn-out' among medical doctors[148] could be interpreted as a warning sign that the convergence of medical technologies and new management technologies is currently creating *an unprecedented technological enframing of the human condition within the healthcare system*. Fortunately (not for medicine, but for my argument), there are other medical thinkers than I who see a problem and, thereby, a great professional challenge, in this area:

[148] The suicide rate among male hospital physicians in Denmark is reportedly three times higher than the average suicide rate among working males in the country. A commenting psychiatrist has explained this by a combination of demanding tasks/decisions and stress, or – alternatively - as due to easy access to knowledge about self-poisoning and drugs among doctors. I leave it open to debate whether existential alienation could play a role in these statistics. Bech M. *Læger har rekord i selvmord*. Politiken 5. jan 2006 (http://politiken.dk/VisArtikel.sasp?PageID=428349).

When medical doctor and Harvard-affiliated quality improvement 'guru' Donald M. Berwick was preparing to go to hospital to have his right knee joint replaced due to arthrosis in 2003, he formulated a short wish list of his personal requirements. This author probably knows better than anyone else in the USA that times have recently been good for quality improvement in health care, particularly in the renowned institutions he can choose to access. Nevertheless, he was deeply concerned about what might now happen to him as a patient. His wish list was as follows (Berwick 2004):

> Don't kill me (no needless deaths). Do help me, and don't hurt me (no needless pain). Don't make me feel helpless. Don't keep me waiting. And don't waste resources, mine or anyone else's.

These requirements seem absolutely just and reasonable, don't they? The problem is that as Berwick wrote this list, he feared:

> Given my requirements, it is not clear that any healthcare institution in the United States will want to take me on as a patient.

How can this be? Berwick explains what he means, asks what can be done, – and also provides an answer, to which I wish to draw attention:

> Despite the good news, [quality] improvement is still happening in pieces. It must take some different level of energy, insight and courage than we have mustered so far to get total quality of care. Where will we find the courage we are going to need?
>
> I propose this: If we are going to care enough to provide really different care, top to bottom, we are going to have to begin seeing patients and their lives not 'out there', but as mirrors of our own lives, 'in here'.

What Berwick is asking for, can perhaps best be 'captured' by placeless and timeless human values, such as compassion, tolerance, a sense of caring, consideration of others, and the responsible use of medical knowledge and power.[149] Berwick does not have Heidegger, Jonas, Taylor or Frank on his reference list, but I believe these thinkers could provide a meaningful philosophical framework for Berwick's worries. What I believe he is observing, although not saying so explicitly, is that the rationally and technologically oriented '*hypervalues' of modernity*

[149] Incidentally, the speach made by the Dalai Lama at the previously mentioned conference of *The Society for Neuroscience* in 2005 (see chapter 9.3.1 for the reference) contains the following passage: "By invoking fundamental ethical principles, I am not advocating a fusion of religious ethics and scientific inquiry. I am speaking of what I call 'secular ethics' that embrace the key ethical principles, such as compassion, tolerance, a sense of caring, consideration of others, and the responsible use of knowledge and power – principles that transcend barriers between believers and non-believers, and followers of this religion and that religion."

(see chapter 9.3.2) that have for decades dominated biomedical *research* (see chapter 2.2) are currently beginning to overtake the ethos of *medical care* in general. Berwick's potential caregivers are thereby – in daily life on the clinical wards – becoming increasingly alienated from the basic truths of what it means to be a human being (Vetlesen 2004) and *to care* for other human beings (Jones 2002). Thus, these professionals are being drawn away from values that have since Hippocrates constituted the basis of professional ethics for medical doctors (see chapter 4.1.1 on professionalism and Appendix 2 regarding Hippocrates).

The capacity for moral imagination has – until now – been central to medical professionalism. And once moral imagination is in place, I believe it automatically opens a global perspective on things (Benatar 2005 ii). Berwick also points this out, whilst contemplating his knee:

> For me it is only a knee. Thank God. It could have been my heart. It could be cancer (…) or a disabling psychosis. (…) I could be not just an American with a bad knee but a Thai with dengue or an African with AIDS.
>
> Therein lies the challenge [for us as doctors]: finding the courage to see myself in others. What if everyone I want to help is just like me, in disguise? (…) I am coming to believe that we cannot relieve the distress of others until we get better at sensing our own, and what we need to relieve it. That may be the only sustainable source of sufficient will for change.

This thesis focuses on preventive medicine as it is currently promoted and practiced in affluent industrialised countries. I however believe, like Berwick, that we will do a more truthful and responsible job locally if we concurrently think globally and consider our professional actions and duties from a wider perspective. Although the 20th century saw a major expansion of the world's economy and spectacular progress in science and technology, the sad reality of the first decade of the new millennium is that human life, well-being and security remain under severe threat – a threat that can be related to a large extent to adverse effects of increasing disparities in wealth, health and knowledge within and between nations (Benatar 2005 i and ii; Benatar et al. 2005). There is, as yet, no explicit and coherent political, social or ethical framework to help nations, in general (Horton 2003), or physicians, in particular (Benatar 2005 i), to cooperate in addressing this challenge. I personally see this as the most obvious and legitimate arena where the medical profession could – and ought to – make deliberate use of the fact that *we are still one of the ma-*

jor remaining sources of taken-for-granted social authority in our times, as described by medical ethicist Richard Zaner (2003). Rather than losing our collective trustworthiness by chasing blood pressure measures, cholesterol levels and other risk factors indefinitely in order to control and "treat" them with drugs, driven by the vanity of Vision Zero, I think we should invest a few more resources in the creation of a shared global understanding of how it might be possible to secure the health of humankind throughout the world (Benatar 2005 i).

To improve human health in a world-wide perspective, there is, however – as I have previously outlined in this thesis – a need for a wider horizon in medical research and an urge to appraise human beings for what they are: persons capable of constructing and maintaining meaning in interaction with others. Nobody is a meaningless body with a mind located somewhere else. Medical research ignoring this perspective is neither up to the challenges it faces nor ethically justifiable. Realising this, medicine should join forces with other academic disciplines; philosophy and ethics, ecology, political science, economics and social geography, to mention just a few (Horton 2003; Ruger 2004 i and ii; Kirkengen: lecture at Rosendal seminar, 2005).

Before the Dalai Lama took the podium at the 2005 conference of *The Society for Neuroscience* in Washington,[150] about 800 people had signed an online petition demanding that his invitation be withdrawn. Outside the conference hall itself, a young neuroscientist held a poster with the words

"DALAI LAMA NOT QUALIFIED TO SPEAK HERE."

In an interview with the press, this scientist maintained that:

> This is supposed to be a scientific talk. If he is not presenting data, he should not speak.

I truly disagree with this scientist. My reasons are in this thesis. It is my hope that the arguments and reflections presented here can – in an academically justifiable manner – be of help to colleagues and others who, for explicit or, perhaps, mostly intuitive reasons, 'know' that medical

[150] This speech was introduced in chapter 9.3.1 and was also mentioned in the previous footnote.

science needs to encompass much more than the collection of original, empirical data. In order to promote sustainable and responsible medical research and practice, I believe we are obliged to regard medical activity from a distance. Not only should medical professionals be called upon to explain their own work (as outlined in chapter 4.1.5), but medical activity should also be examined and challenged from other intellectual viewpoints. Closing the discussion of this thesis, I think the most important thing I have learnt is to appreciate what Hans Jonas, profoundly aware of the potential of ever more sophisticated medical technology and the ever increasing status derived from it, meant when he formulated the core of his concern as follows (Jonas 1974, as quoted in Zaner 2003):

We need wisdom most when we believe in it least.

END

EPILOGUE

On existential ground

I believe there is no such thing as objectivity and value-neutrality in human life. Whilst working on this thesis, I have come to realise how my own background and closest family have influenced the way I relate to modern medicine with its strengths, limitations and fascinating paradoxes. I want to express my gratitude:

To my father Jan R. Getz (1921-1997)
Even after you became an internationally renowned researcher in the field of shipbuilding and marine construction (and were awarded the Royal Norwegian Order of St. Olav), you always kept a pencil and a folded sheet of paper in the back pocket of the saggy pants you loved to wear when out-of-office.

It was the 27th of March 1980, and I was 17 years old. On that stormy day, the oil platform Alexander L. Kielland broke and turned over. 123 people died; 89 survived. You were in no way professionally responsible for what happened, but I shall never forget the look on your face in the days following the catastrophe. There was the disbelief and emptiness which we all felt. But there was more, something unfamiliar. Today, I think it was the look of remorse, as if you felt responsible for not having acted upon a gut feeling that something was wrong. Gradually, I realised that you had been concerned about the lack of safety in the North Sea long before the disaster struck. This hypothesis was strengthened in the spring of 2005, 25 years later, when historian Helge Ryggvik described the Kielland event in terms of "An announced disaster" (En varslet storulykke, see *Petromagasinet* 1/2005 or *Dagbladet* 15. mars 2005.) Observing you in the days after the event taught me, I think, that *if something feels wrong in your professional environment, one has to speak out*. Internal professional critique is not necessarily welcome, however. You knew, or at least you would sometimes say: "You are right; you ought to be hanged," when someone said something unpleasant, but relevant.

The Alexander L. Kielland saga also taught me the virtue of *sound scepticism in the presence of expert authority*. When the Norwegian Par-

liament finally succeeded in convincing the government to take "full responsibility" and request the Kielland platform to be reversed from its overturned position at sea, your back-pocket pencil immediately came out. After making a quick sketch and contemplating the engineering task at hand, you concluded: "It cannot work." I remember my bewilderment as I said "But Dad, the plan is designed by experts!" "I am afraid," you said, "that it still won't work." And it turned out that you were right.

Your final year was dramatic from a medical point of view. Well into retirement, you still fixed everything around the house yourself. Then, in the summer of 1996, you fell from the roof. The head injury was almost fatal. But you survived, with severe brain damage. One year later, you walked the streets of Trondheim, on your way to an old friend's funeral. You were dressed in a ragged outfit you had been wearing when painting the house some years earlier. Objectively speaking, you should not have been on you own, or dressed the way you were. But nobody (not my mother, whom you had always loved sincerely, nor any health institution - it had certainly been attempted) could stop you from doing what was important to you. Then you stumbled and fell, and acquired a fracture of the neck (dens axis), which paralysed your body from the neck down.

You managed to hang onto life until I arrived from Iceland. I was eight months pregnant, expecting my first child. At the Intensive Care Unit, they had started to give you nutrition i.v. when I arrived. I immediately asked to see the anaesthesiologist on duty and protested angrily to this absurd treatment. The doctor replied quite calmly: "Don't worry. There is much more between heaven and earth than we know. In this situation, I don't think the nutrition will interfere with those things."

That was a wise reply. It encouraged me to concentrate on the important things. So I went back to your bed, sat down and stroked your chin, – the only part of your body with sensibility still intact. You were intubated and could not speak, but your bewildered eyes brought forward a very clear question, which I was able to answer honestly: "Yes, Dad. I am happy with my life in Iceland. It is not easy, but it will be OK. When I was a little girl, I thought I would never be able to live without you. But… now I know I will manage quite well.

So Dad…. you are free to let go, if that is what is best for you."

Early the next morning, Stefi, your wife, sat beside your bed for a couple of hours. Then she felt that you needed to rest. Soon after she left the hospital, your heart quietly stopped beating.

To my mother Stefi Getz, nee Okkenhaug (1923 - Dec 25th 2004)
Looking back to my childhood, I had the best mother of all. You were so attentive, so intuitive, so generous – and so elegant. Despite being older than the mothers of my peers, you were the one who opened the house to the kids of the block. You *saw* people. My friends from school and university would drop in to see you, even the week before you died! I also remember the pride I felt upon seeing you accompany Jan to gala dinners arranged by the shipping industry. It was not until I became an adult that I started to reflect upon the more subtle sides of my childhood: Why did I always get so angry and care so little for you during the few days you ever spent in bed, sick with something like flu? And why would I never sit in your lap?

Today I realise that the answers to these minor, but significant, questions are embedded among three letters: *Tbc*. During the war, you were involved in the resistance movement in Trondheim. This brought you to prison. Your cell mate was severely ill and coughing. You helped her as best you could. When I was born two decades later, you had survived two bouts of life-threatening tuberculosis. As a person who had experienced, and embodied, the true meaning of *medical stigma*, you did not encourage children to come close. And surely, it makes sense that you could not handle trivial illness lightly. Thus, simple flu could fill your bedroom with darkness and surrender, totally out of proportion to the situation. No wonder I stayed out.

I owe my life to medical advance. You said that you took the decision to have a second child at a mature age only because your physician promised that Tbc could now be cured with drug therapy, should it recur. You would never have to experience again what happened six weeks after the birth of your first child, my sister Ingri.

I never had the courage to *listen deeply* to that story. You were first admitted to a sanatorium filled with people in the final stages of Tbc. What was it *really* like? The doctors refused to let you see your newborn child for months and months. In response to your trembling question, the

young doctor bluntly said: "If your baby has been infected, let us hope she will die quickly, because it [Tbc] has a tendency to go to the head of those little ones [referring to meningitis]". How was it to undergo thoracoplasty in those days? And how did it feel to be discharged, filled with hope – only to be readmitted again a few years later, with almost all hope of survival gone. I never invited you to share the pain, and you were wise enough never to push it.

You died peacefully in the silence of Christmas night in 2004. The night warden at the old people's home reported that you had been a little restless around 3:30 a.m. For no obvious reason, you asked her just to "be there." And then you died. The staff was struck by a blend of surprise and awe.

Together with my family, I had come over from Iceland to visit you only one week before you died. There were no objective medical signs of imminent death at that time. But when we said goodbye, you looked me briefly in the eyes in a way that was new to me. And during the next days, it sunk in. I knew. Your life was about to come to an end.

I have never been much for listening to sermons, but I felt a strong urge to listen to the midnight mass on Icelandic television on Christmas night, four days after returning from Norway. The Bishop of Iceland has a remarkably determined and gentle voice. I remember quite distinctly that he said:

"*Nú er heilög jólanótt, þegar himinninn snertir jörðina á sérstakan hátt.*"[151]

I also remember the silence that followed, and the way I shivered.

[151] Icelandic: "This is the Holy Night, when Heaven touches the Earth in a particular way."

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PAPER I

PERGAMON

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Ultrasound screening in pregnancy: advancing technology, soft markers for fetal chromosomal aberrations, and unacknowledged ethical dilemmas

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Abstract

Fetal ultrasound screening has become routine practice in many western countries. During the last decade, such screening has led to frequent situations characterised by clinical uncertainty due to the disclosure of soft markers in the unborn child. Soft markers are minor anatomical variations indicating a somewhat increased likelihood that the fetus has a chromosomal aberration, most frequently trisomy 21 (Down syndrome). This paper presents the results of a comprehensive literature search of the National Library of Medicine with emphasis on the chronological development of scientific knowledge in relation to soft markers and the link between advancing imaging technology and clinical counselling dilemmas. An analysis of the literature makes evident that many ultrasound examiners have counselled individual pregnant women on the basis of insufficient data. Moral dilemmas have thus emerged as a direct result of advancing medical technology, and healthy fetal lives prove to have been lost due to invasive diagnostic testing aimed at resolving clinical uncertainty. Ultrasound examiners have warned against a policy of disclosing all findings of soft markers to expectant parents, but no exploration of experiential aspects linked to the disclosure of fetal soft markers has yet been published in the medical literature. The emotional reactions of mothers are important to consider given their potential impact on the biological development of the fetus.

In conclusion, this paper stresses the need for paying close attention to the crucial distinction between technology development and technology implementation in relation to prenatal testing. Furthermore, it provides strong arguments for scrutinising the interface between prenatal testing and human experience.

Keywords: Ultrasound screening; Soft markers; Chromosomal aberrations; Nuchal translucency; Down syndrome; Ethical dilemmas

Through a decade of disclosing soft markers indicating an increased risk for chromosomal aberrations in the fetus, obstetric medicine has contributed to the emergence of new and complex clinical and ethical dilemmas.

> Situated on a research frontier of the expanding capacity for prenatal genetic diagnosis, they (women) are forced to judge the quality of their own fetuses, making concrete and embodied decisions about the standards of entry into the human community. Rayna Rapp (2000)

In this paper, we attempt to describe the origin and nature of these dilemmas as well as their impact on the persons involved. It is our aim to elucidate sensitive issues related to routine obstetrical practice that are relevant to both professionals and lay persons. We first consider the implications of ultrasound screening as it is routinely offered during the second trimester. However, there is currently a trend towards supplementing or

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replacing second-trimester ultrasound with ultrasound screening between gestational weeks 11–14. So-called early ultrasound (see for example Nicolaides, Sebire, & Snijders, 1999) will be considered in the second section of the review.

Ultrasound screening in the second trimester

Ultrasound screening is widely offered to all pregnant women in pregnancy weeks 17–20, and obstetricians express great enthusiasm for ultrasound as a tool for enhancing individual reproductive choice (e.g., Economides, 1999; Economides, Whitlow, & Braithwaite, 1999; Nicolaides, 1998). Ultrasound holds a special position among prenatal tests because many people report that 'seeing' the fetus on the ultrasound monitor is an emotionally rewarding experience (Baillie, Mason, & Hewison, 1997; Clement, 1998; Eurenius, Axelsson, Gällstedt-Fransson, & Sjödén, 1997). Whatever their views about prenatal diagnosis, most expectant parents accept ultrasound screening for purposes such as gestational age, 'seeing' the baby and receiving 'general reassurance' that the baby is intact and alive (Baillie, Hewison, & Mason, 1999; Baillie, Smith, Hewison, & Mason, 2000; Chudleigh, 1999; Dornan, Harper, & Bailie, 1998; Thornton, Hewison, Lilford, & Vail, 1995).

The net medical benefit of ultrasound screening, measured in terms of maternal and fetal mortality and morbidity, is still subject to controversy (Bricker et al., 2000; Enkin et al., 2000). Researchers have evaluated its potential effect on health behaviour changes, such as reduced maternal smoking, but the results are inconclusive (Baillie et al., 1999; Chudleigh, 1999). The argument that prenatal ultrasound screening is founded more on the capability of the technology and related expertise rather than on its objective benefit to public health (Oakley, 1993) remains open to debate.

The scope of prenatal ultrasound screening has undergone significant changes since it was introduced in the 1980s. Its original goal was to reduce obstetric risk by enhancing safety for mother and child, correcting gestational age, locating the placenta, and diagnosing twin pregnancies. As imaging technology developed and societal expectations changed, there has been an increasing focus on fetal diagnosis, namely disclosure of structural abnormalities in the unborn child (Bricker et al., 2000; Dubbins, 1998; Filly, 2000; Griffiths & Gough, 1985). Until the early 1990s, it was feasible to disclose major structural fetal malformations, such as a missing brain (anencephaly) or open abdomen (gastroschisis). As a result of refinements in technology, clinical training and expertise, disclosure of more subtle structural abnormalities such as a cleft lip is currently possible.

During the last decade, many attempts have been made to screen for fetuses with chromosomal (caryotypic) aberrations, particularly trisomy 21 (Down syndrome) (e.g., Baillie & Mason, 1997; Nicolaides, Snijders, Gosden, Berry, & Campbell, 1992). In relation to Down syndrome, screening by second-trimester ultrasound has not proved successful, as we will document.

A state-of-the-art routine prenatal ultrasound examination currently involves obstetric risk reduction, fetal diagnosis and attempts to screen for chromosomal aberrations. Each of these areas raises separate ethical concerns. In practice, it is not possible to pursue these concerns selectively, as the monitor reveals information related to the different aims simultaneously. At most ultrasound centres, screening is offered as an 'all-or-none' package because examiners consider it unrealistic and unethical not to report anomalies that may 'leap to the eye' (Fitzgerald, 1999). However, because a number of markers are not clearly associated with fetal problems, clinical uncertainty and false positive identifications arise.

Clinical uncertainty and false positive findings

The rapid advance of imaging technology has led to considerable clinical benefit, but has also generated diagnostic ambiguities and confusion in several areas of medicine (Black & Welch, 1993; Cassell, 1993). Progress in ultrasound imaging techniques in the 1980s led to a series of new discoveries in relation to fetal anatomy (Griffiths & Gough, 1985) that posed unexpected difficulties for examiners involved in the interpretation and communication of findings related to fetal anatomy (Furness, 1987; Lumley, 1990).

From the beginning of the 1990s, diagnostic uncertainty reported by ultrasound examiners has often been related to the disclosure of so-called anatomical soft markers. The term 'soft marker' was coined around 1990. The current definition of soft markers is (Bricker et al., 2000):

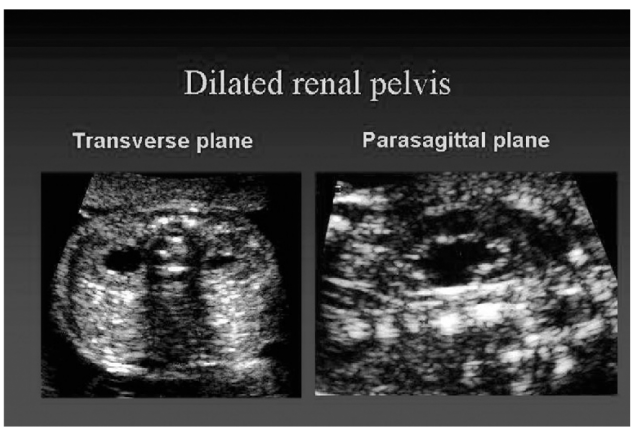
> structural changes detected at ultrasound scan which may be transient and in themselves have little or no pathological significance, but are thought to be more commonly found in fetuses with congenital abnormalities, particularly caryotypic abnormalities.

It is important to note that soft markers are qualitatively different from actual structural abnormalities (Bricker et al., 2000). The markers are mainly of interest because of their statistical association with chromosomal aberrations, an association that makes them potential identifiers of these conditions (Nicolaides et al., 1992). Soft markers that can be detected by a second-trimester ultrasound scan include choroid plexus

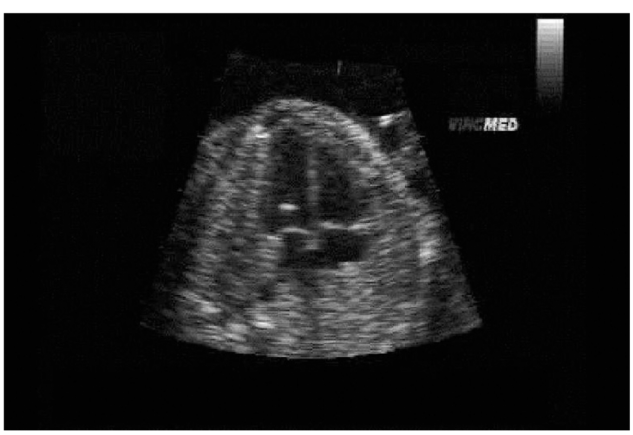
cysts (CPCs), renal pelvic dilatation, echogenic foci in the fetal heart (visualised as circular white dots, thus nicknamed 'golf balls') or fetal gut (echogenic bowel), short limbs and nuchal thickening. Most, but not all soft markers (e.g., not CPCs) are associated with an increased risk for trisomy 21 (Down syndrome). Several soft markers may co-exist within the same fetus, and systems for scoring combinations of different markers have been developed (Benacerraf, Nadel, & Bromley, 1994; Bromley, Shipp, & Benacerraf, 1999; Farina, Malone, & Bianchi, 2000). Even in the presence of two markers, the adjusted risk of Down syndrome has generally been known to be low in absolute numbers. It may for instance be 1:100, which is still a significantly increased risk from the perspective of fetal medicine. In many countries, an invasive diagnostic procedure is generally offered when the estimated risk is in the range of 1:300 or higher, corresponding to the chances of giving birth to a child with Down syndrome associated with a maternal age of 35–36 years. The invasive procedures, chorionic villus biopsy or amniocentesis, carry a risk of fetal loss in the range of 1:100 (Enkin et al., 2000). If a chromosomal aberration is confirmed by invasive testing, the 'therapeutic' options are to terminate the pregnancy or to prepare for the arrival of the child.

Slides 1 and 2 are two ultrasound images of anatomical soft markers which indicate a slightly elevated risk that the fetus has Down syndrome.

As a result of the medical field's interest in soft markers, a steadily increasing amount of data related to anatomical soft markers has been released, often from



Slide 1. Mildly dilated renal pelvis.



Slide 2. Fetal heart with echogenic cardiac focus.

referral centres with the latest in ultrasound equipment. The first descriptions of structural variations that were later to gain status as anatomical soft markers appeared in the second half of the 1980s. Following the identification of a new marker, a number of publications would discuss its significance. To document the rising interest in soft markers, we adapted Skolbekken's method (Skolbekken, 1995). We searched the medical literature (National Library of Medicine) for peer-reviewed papers related to the five most discussed soft markers from 1982 to 1999. The number of publications is presented in Fig. 1. Key words were: fetal CPCs, echogenic bowel, echogenic cardiac foci, mild renal dilatation and nuchal translucency. Different terms describing the same soft markers (such as nuchal oedema and pelvic dilatation) were also employed in the search strategy, since various terms were applied to each marker until consensus regarding terminology was reached. Titles (and abstracts, when accessible) of all publications were checked to ensure relevance to the topic.

Despite this flurry of research publications, ultrasound screening with the help of soft markers is still fraught with clinical uncertainty. Truly false positive findings of major fetal abnormalities rarely occur when ultrasound screening is performed by an expert (Boyd, Chamberlain, & Hicks, 1998; Isaksen, 2000). In the context of prenatal ultrasound, the term *false positive finding* generally refers to the assignment of an 'at-risk' label to a fetus that is subsequently found to be clinically normal.

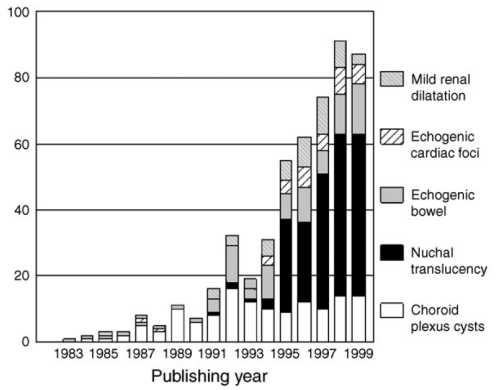


Fig. 1. Number of papers in relation to the five most investigated soft markers published per year as a function of time. Note the first scattered observations of each new marker (often not linking the marker to chromosomal aberrations) in the 1980s. As the relation to chromosomal aberrations was established, a rapid increase in publishing typically followed. Note: The term nuchal translucency relates to early pregnancy (week 11–14), but originated as a finding at second-trimester ultrasound (designated nuchal thickening or fold). The remaining markers relate to second trimester screening (week 17–20).

Estimations related to the pathological significance of a new soft marker have generally been conflicting to begin with, conclusions ranging from the marker being 'a normal finding' to 'an indication for amniocentesis'. Most of the controversy regarding soft markers has surrounded the presence of isolated soft markers in younger (low-risk) women (Bricker et al., 2000). Several expert examiners have reported that ambiguity in relation to the marker's clinical significance has resulted in confusion, uncertainty and counselling dilemmas, particularly as examiners working with low-risk populations had to make comparisons with data collected on high-risk pregnancies at referral centres (Baillie et al., 1997; Bricker et al., 2000; Dubbins, 1998; Filly, 2000; Whittle, 1997). The marker *mild renal dilatation* can be used as a first example: an up-to-date examiner would read about an association with Down syndrome in 1990 (Benacerraf, Mandell, Estroff, Harlow, & Frigoletto, 1990). From 1996 s/he would have access to data documenting that mild renal dilatation occurs in 1–2% of fetuses in an unselected population (Morin et al., 1996; Whittle, 1997) and that the finding seldom has any major clinical significance (Malone, 1996; Morin et al., 1996). These facts might seem reassuring to most lay people, but the expert clinician still faces the dilemma of whether to inform the expecting parents, as the absolute risk for Down syndrome still remains slightly elevated in the presence of mild renal dilatation.

Another example of soft markers being prematurely introduced in parental counselling relates to *choroid plexus cysts* in the fetal brain. These were first described as a normal finding in 1984. The subsequent literature revealed a lot of controversy: CPCs were for a period of time linked to an increased risk of Down syndrome, but by 1995 it was documented that this association was very weak (Dubbins, 1998; Filly, 2000; Whittle, 1997). Scientifically up-to-date ultrasound centres subsequently refrained from offering invasive testing to young women whose fetuses had one small CPC. Some examiners stopped informing expecting parents of such findings, as they wanted to avoid unnecessary anxiety (Baillie et al., 1997; Dubbins, 1998; Filly, 2000; Whittle, 1997).

Until the year 2001, only one published study (Boyd et al., 1998) had documented the impact of the detection of ultrasonographic soft markers on the efficacy of prenatal screening programmes (Bricker et al., 2000). This study was based on an unselected British population and documented that between 1991 and 1996, the identification of ultrasonographic soft markers led to a 4% increase in the detection of fetal malformations, from 51% to 55%. This development was accompanied by a 12-fold increase in the false positive rate, which rose from one in 2332 to one in 188 pregnancies during the study period. This finding generated questions concerning resource allocations, risk of procedure-related pregnancy loss, and the short- and long-term

psychological impact on expectant parents (Boyd et al., 1998; Bricker et al., 2000).

Clinical practice related to disclosure of soft markers at second-trimester ultrasound has been poorly explored and documented. Published data are very scarce, but available information indicates that clinical practice varies considerably, according to technology, definition, examiner, national legislation and the medico-legal context. In Great Britain, an estimated 2% of pregnant women receive a risk label on the basis of soft markers detected by ultrasound (Baillie et al., 2000). A recent publication shows a wide variation in both knowledge and management strategies related to soft markers among British ultrasound centres (Maclachlan, Iskaros, & Chitty, 2000). The authors conclude that

> …the variation in management reported here is not acceptable and can lead to confusion both amongst professionals as they move from one unit to another, and in women cared for in units with different policies. There are also implications with regard to litigation, which is perhaps why some units do not document the findings of these markers when they do not intend to discuss caryotyping.

Norwegian legislation in relation to prenatal diagnostic testing is rather restrictive. A routine offer of caryotyping (amniocentesis) is available only to Norwegian women 38 years and older. At the National Centre for Fetal Medicine in Norway, approximately 1% of women originally classified as 'low-risk' are currently offered invasive testing on the basis of soft marker disclosure at second-trimester ultrasound screening. This management strategy is derived from a risk scoring method that combines and weighs maternal age, family history, and the presence of eventual soft markers. In general, the Norwegian experts advocate information and counselling about an increased risk for fetal trisomy 21 only if two or more risk factors, including advanced maternal age, are present (Kjell Å. Salvesen and Sturla Eik-Nes, personal communication, 2001).

In the United States, soft markers seem to be dealt with very differently. Due to the probability of litigation, examiners report that they have no choice but to inform their clients about all findings of fetal soft markers. In the year 2000, two American experts independently reported that at least 5-10% of low-risk women who entered their practices would end up with an 'at-risk' label as they received information about the presence of one or more ultrasonographic risk markers in their fetus (Benacerraf, 2000; Filly, 2000).

More harm than good?

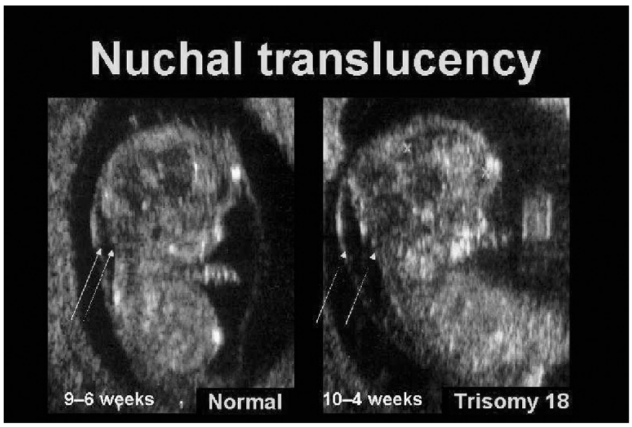
Smith-Bindman and colleagues reviewed a decade characterised by an increasing interest in anatomical soft markers for fetal chromosomal aberrations in a meta-analysis concerning the efficacy of second-trimester ultrasound screening for Down syndrome (Smith-Bindman, Hosmer, Feldstein, Deeks, & Goldberg, 2001). After reviewing all available evidence concerning seven different soft markers, the authors concluded:

> Because the use of these (soft) markers may be associated with more harm than benefit, clinicians should be very cautious about the use of these markers to counsel women about their risk of having a fetus with Down syndrome.

The analysis showed that six of the seven markers studied were associated with a positive predictive value for Down syndrome in the range of only 0.2–1%. This means that the risk that an 'average' fetus which exhibits such a marker will actually have Down syndrome lies in the range of 1:500 to 1:100. Due to the risk of abortion associated with invasive diagnostic testing (the only option for a woman who wants to clarify the situation), one to four women will lose a healthy fetus for each diagnosis of trisomy 21 that is confirmed. The seventh soft marker included in the study was thickening of the fetal nuchal tissues, a marker described by Szabo and Gellen in 1990. It showed somewhat better test characteristics; the positive predictive value of nuchal thickening was 2.4%. It could thus be calculated that 'only' 0.6 healthy fetuses would be lost for each confirmed case of trisomy 21. The authors nevertheless concluded that this marker, although more reliable, was inappropriate for the purpose of screening fetuses with Down syndrome in the second trimester of pregnancy.

First-trimester ultrasound screening

During the mid- and late 1990s, systematic research gradually confirmed the advantages of ultrasound in early pregnancy, i.e. between gestational weeks 11 and 14, as compared to the second-trimester (Nicolaides et al., 1999; Pandya, Snijders, Johnson, de Lourdes Brizot, & Nicolaides, 1995). At this time, the soft marker nuchal thickening (sometimes called nuchal fold) was found to have better test characteristics as a screening parameter for chromosomal deviations. In early pregnancy, the phenomenon of nuchal thickening has formally been designated nuchal translucency. Nuchal translucency can be defined as 'the maximum thickness of the subcutaneous translucency between the skin and the soft tissues overlying the cervical spine' as measured by ultrasound (Snijders, Noble, Sebire, Souka, & Nicolaides, 1998). Based on a standardised measurement of fetal nuchal translucency, an 11–14-week ultrasound scanning procedure is currently being launched in several countries (Nicolaides et al., 1999). A computer



Slide 3. Left: Nuchal translucency—normal. Right: Nuchal translucency—increased.

program provides an individualised risk estimate for Down syndrome and trisomies 13 and 18, by combining maternal age and family history with measures of fetal size and nuchal translucency obtained by ultrasound (see Slide 3).

False positive findings

In a normal population, Down syndrome is diagnosed in approximately 1:700 births. It is well documented that 75–80% of fetuses with Down syndrome can be detected by early ultrasound (test sensitivity), at a false positive rate of about 5% (1-specificity) (see for example Economides et al., 1999). It is easy to calculate that targeted invasive testing of fetuses which exhibit increased fetal nuchal translucency early in pregnancy may reduce the number of healthy fetuses lost for every confirmed case of trisomy, as compared to screening based on maternal age or second-trimester ultrasound. As opposed to second-trimester ultrasound screening, early ultrasound screening is thus being explicitly promoted as screening for Down syndrome.

The accuracy of early ultrasound screening (sensitivity, specificity and positive predictive value) can be enhanced by combining ultrasound with maternal serum tests in the computerised risk estimate (Spencer, Souter, Tul, Snijders, & Nicolaides, 1999; Wald, Watt, & Hackshaw, 1999). One such combined test is the One-stop clinic for assessment of risk (OSCAR) which implies one visit to the clinic that can ideally be completed within 60 min. One year's experience by a British centre offering the OSCAR test showed a screening uptake of 98% and an 86% detection rate for fetuses with trisomy 21. The rate of false positive test results was 5.5% (Spencer, Spencer, Power, Moakes, & Nicolaides, 2000). Among the approximately 4000 pregnancies monitored during that year, 5–6 children with Down syndrome would expectedly have been born in the absence of prenatal testing.[1] For each child to be diagnosed, it can be calculated that 30–40 expectant couples received information about an increased risk for Down syndrome and underwent invasive diagnostic testing.

A number of countries have an established tradition for prenatal screening for Down syndrome by way of maternal serum testing. A false positive finding in such a test can, somewhat simplified, be explained by the fact that some test results will necessarily be situated beyond a defined cut-off point on the tail of the normal distribution curve, even in the absence of pathology. Anatomical soft markers, particularly increased nuchal translucency, cannot be interpreted, explained and communicated to expectant parents in the same way. This is because increased nuchal translucency is also associated with a number of other conditions than the primary targets of screening which are trisomy 21 (Down syndrome), 18 (Edward's syndrome) and 13 (Patau's syndrome). Increased nuchal translucency may for instance be related to non-lethal chromosomal aberrations that would not be clinically recognised by

[1] The number of fetuses present at screening will be 30–40% higher, as many fetuses with trisomy 21 die spontaneously between week 10 and birth (Hyett, Sebire, Snijders, & Nicolaides, 1996; Morris, Wald, & Watt, 1999). In the actual study, six fetuses with trisomy 21 were detected by screening. One died spontaneously shortly after invasive diagnosis, whilst five were selectively aborted. One fetus was missed by the screening and resulted in the live birth of a child with Down syndrome (false negative screen result).

most lay people, as well as to major structural malformations such as cardiac defects[2] and diaphragmatic hernia. These can usually be ruled out by ultrasound late in the second trimester. But even if no diagnosable condition is confirmed by invasive testing and subsequent targeted ultrasonic investigations, an association with rare genetic syndromes as well as unexplained fetal death has been reported (Adekunle, Gopee, el-Sayed, & Thilaganathan, 1999; Hyett, Perdu, Sharland, Snijders, & Nicolaides, 1999; Nicolaides et al., 1999; Souka, Snijders, Novakov, Soares, & Nicolaides, 1998). The prevalence of unfavourable outcomes among fetuses with increased nuchal translucency in the presence of normal chromosomes has been reported to be as high as 30% (Bilardo, Pajkrt, deGraaf, Mol, & Bleker, 1998), whilst other studies indicate a more favourable prognosis (Pajkrt, Mol, Bleker, & Bilardo 1999; van Vugt, Tinnemans, & van Zalen-Sprock, 1998).

The clinical efficacy of early ultrasound screening is currently being subjected to scientific evaluation in several countries. In the year 2000, a British panel of experts concluded that there is need to await further scientific documentation before early ultrasound screening is introduced on a routine basis (Bricker et al., 2000). A Swedish panel of experts assessing the method in 2001 came to the same conclusion (SBU, Saltvedt, & The-Hung Bui, 2001). Despite the reluctance of experts, official plans to introduce nuchal translucency screening for general populations are being launched (Alderson, 2001; Getz, 2001). This development calls for debate on the ever more blurred distinction between medical actions aiming at *knowledge production*, conceptualised as being 'value neutral', and medical actions aiming at *clinical intervention,* representing a clearly value-laden application of presumably value neutral knowledge.

Professional dilemmas, maternal distress, and the maternal–fetal relationship

In contrast to the social sciences that equate enhanced knowledge sophistication with complexity and ambiguity, biomedical diagnostic technologies seek enhanced sophistication through the reduction or even elimination of ambiguities (Cassell, 1993). The history of ultrasonographic soft markers may be deemed as an outstanding example of such efforts. Each of the soft markers appears to have its rise and fall. CPCs were discovered in 1984 and were applied in clinical counselling until about 1995 when they were found to be unsuitable as screening parameters in relation to Down syndrome. Mild renal pelvic dilatation gained similar attention from 1990 to approximately 1997, and echogenic cardiac foci from 1994 to 1999. Since 1995, increased nuchal translucency has gained attention as the most promising marker in prenatal screening for Down syndrome. But moral dilemmas have not been eliminated by these latest advancements in prenatal diagnostic technology. Uncertainty linked to, or even created by ultrasonographic findings has always been present, although its sources have varied. Furthermore, it appears that technological advancements will allow the study of fetal development to take place at even earlier stages in the near future (Blaas, Eik-Nes, Berg, & Torp, 1998), perhaps introducing more private moral dilemmas for pregnant women and expecting parents. The dilemma confronting both the ultrasound examiner and the mother will now be discussed.

Assigning the risk label: the examiner's perspective

In 1987, an examiner conducting fetal ultrasound scanning on a routine basis described the uncertainty of her work as 'walking blindfold in tiger country' (Furness, 1987). The author underlines how ultrasound can never offer complete certainty, whilst any hint of uncertainty may have a devastating effect on expecting parents. Despite the fact that several ultrasound examiners have expressed concern over this topic in recent years (Boyd et al., 1998; Dornan et al., 1998; Dubbins, 1998; Filly, 2000; Whittle, 1997), no empirical research addressing the experience or behaviour of fetal ultrasound examiners in relation to diagnostic uncertainty is available in the medical literature.

From the moment an increased risk for fetal abnormality has been disclosed and explained to the expectant parents, the biomedical ideals of 'non-directive counselling' and 'free reproductive choice' indicate that the health professional should retreat from his or her usually active expert position and allow the expectant parents to evaluate the situation under minimal external pressure (Biesecker & Marteau, 1999). Medical information about the unborn child, considered as value neutral within the biomedical paradigm, is thus transformed into a profound and private moral dilemma. In contrast to other medical screening programs that are not associated with similar moral dilemmas, it appears that the role of a fetal screening expert is far better tailored to ruling out anomalies than to the situation of suspecting or identifying them.

Research within other medical settings documents that physicians vary significantly in their self-reported willingness to disclose uncertainty, and that this variation is reflected in their communication with patients (Gordon, Joos, & Byrne, 2000). To most western clinicians, respect for patient autonomy implies that the physician will disclose any information that s/he believes to be of relevance to the individual. The

[2] Expert clinicians already consider cardiac defects among the 'target' conditions in relation to early ultrasound screening.

paternalistic doctor who 'protects' patients from what s/he believes to be an unreasonable burden to carry (the classic example being a cancer diagnosis) is on the retreat even in countries with a strong tradition for keeping bad news from patients (Mitchell, 1998). As previously mentioned, clinicians who practise in a context where litigation in the wake of a 'wrongful birth' is known to occur have little choice but to inform about all soft markers.

More and more, the efficacy of medical procedures and interventions are being subjected to critical scientific evaluation. Obstetrics has been among the best-investigated areas, as illustrated by the meticulous data reviews performed by the Cochrane collaboration. Within the biomedical paradigm, however, the recognised end-points in relation to fetal screening and diagnosis are limited to maternal and child mortality, physical morbidity, and detection rates (for a discussion of this, see Oakley, 1993). Authorities within the renowned tradition of evidence-based medicine have to a certain extent expressed a need for scientifically valid studies of human experience to support outcome studies based on 'hard' end-points (Sackett, Haynes, Guyatt, & Tugwell, 1991), but as yet, the medical profession has no established tradition for conducting such research, nor for inviting scholars from academic disciplines to contribute 'evidence' (Getz, 2001). The steadily advancing biomedical literature on prenatal testing does not address the powerful social norms that are evoked in a setting where human conditions are defined in terms of 'normal' and 'abnormal' (Ettorre, 2000; Hubbard, 1995; Kirkup & Smith Keller, 1992; Lippman, 1991; Press, 2000; Root & Browner, 2001).

Being-at-risk: the perspective of the expectant woman

There is a vast discrepancy between the scientific term *population-based risk* and the social term of *risk perception*—the experience of being-at-risk. To the clinician, risk retains the character of a population-based number, but to the individual pregnant women, the population base is one, herself, and 'one in a hundred' means that she can be the one (Baillie et al., 2000; Roelofsen, Kamerbeek, & Tymstra, 1993). Information about a small increase in risk may thus evoke an emotional response corresponding to an absolute risk of 50% (Adelsvärd & Sachs, 1996; Baillie et al., 2000). Filly notes that an increasing number of women in his practice appear to become emotionally 'trapped' by a medical test procedure to which most of them consented with expectations of a rewarding experience and expert reassurance (Filly, 2000).

In the context of maternal serum screening for Down's syndrome, a number of studies have documented considerable maternal distress in relation to false positive test results (Marteau, et al., 1992; Rausch, Lambert-Messerlian, & Canick, 2000; Salonen, Kurki, & Lappalainen, 1996; Santalahti, Latikka, Ryynänen, & Hemminki, 1996; Statham & Green, 1993). Very little empirical research has, however, addressed parental experience of the detection of anatomical soft markers by prenatal ultrasound. The only published study which we have identified (Baillie et al., 2000) describes in-depth interviews with 24 women who were referred for expert evaluation after a fetal soft marker had been disclosed at second-trimester ultrasound screening.

The study clearly validates the above-mentioned reports from ultrasound experts who have noted that the identification of fetal soft markers can be profoundly distressing for pregnant women. Many interviewees perceived that the disclosure of a soft marker left them with almost impossible choices and had created a state of alienation and crisis which most felt compelled to resolve. They thus opted for invasive testing, such as amniocentesis although such a procedure introduced an even higher risk of losing a healthy fetus than of confirming a chromosomal aberration. In the words of one of the women in the study: 'They said it was 100 to 1 chance, (…) but I couldn't, I wanted to know, you know, it was bad enough waiting for 24 hours, but I couldn't go through the rest of the pregnancy not knowing, I had to know'.

The presence of soft markers made a majority of women put their pregnancy 'on hold' whilst waiting for results of invasive testing; one woman described how she literally closed the door to the baby's room. A similar phenomenon is well documented among women who undergo amniocentesis due to known risk factors such as advanced maternal age, and has been designated 'the tentative pregnancy' by Rothman (1993). In relation to soft markers disclosed by ultrasound screening, the situation of 'tentativeness' arises unexpectedly and abruptly, and Baillie noted how attempts to establish emotional distance from the fetus was often accompanied by feelings of confusion, alienation and ambivalence.

Among women in the Baillie study, the experience of uncertainty regularly predisposed for long-lasting distress, even after the ruling out of a chromosomal aberration by invasive testing. Two-thirds of women experienced some form of residual anxiety that they connected to the soft marker, a distress that they often expressed in terms of a generalised feeling that 'something unexpected' might go wrong with the pregnancy. In comparison, a recent Dutch study showed that 13% of women whose serum screen test was abnormal reported continued anxiety throughout pregnancy even after receiving a normal result of invasive testing (Weinans et al., 2000). The persistence of parental worry has also been reported after the disclosure of false positive results for congenital hypothyroidism in newborns (Tymstra, 1986). Tymstra showed that parental

worries tended to recur later, triggered by events such as illness of the child or a new pregnancy. Several studies refer to the presence of a 'vulnerable child syndrome' in the wake of disease risk labelling or other events during pregnancy, birth or infancy that imply a threat of separation or loss, as the parents may perceive of their child to be particularly vulnerable to illness or injury (Burger, McCue Horwitz, Forsyth, Leventhal, & Leaf, 1993; Kemper, Forsyth, & McCarthy, 1990; Thomasgard & Metz, 1995).

Several authors have discussed the difference between perceptions of risk based on statistical information about a group to which you belong (e.g., pregnant women of 'advanced' age), as compared to a risk derived from a test performed on your living body (Kavanagh & Broom, 1998; Kenen, 1996; Ogden,1995; Roelofsen et al., 1993). Following this train of thought, it may be worth investigating whether the intensity and quality of expectant women's reactions to the presence of a 'visible' fetal soft marker differs from the experience of a false positive serum screening result derived from a maternal blood sample and expressed in abstract, numerical terms. Some of the interviews in the Baillie study (2000) indicate that the visual nature of fetal soft markers may have a persisting impact on an expectant mother's perception of her child-to-be.

The maternal–fetal unity: affecting the core of human relatedness?

From an immunological viewpoint, pregnancy integrates two different individuals under the same skin (Austgulen & Arntzen, 1999). The 'maternal recognition of pregnancy' (Duc-Goiran, Mignot, Bourgeois, & Ferre, 1999) features an acceptance of non-self that defies the rules of immunology that are decisive in every other context (Johnson, Christmas, & Vince, 1999). A general connection between neural processes and immunological responses is well documented (Downing & Miyan, 2000; Petrie, Booth, & Pennebaker, 1998), and there are several psycho-immunological mechanisms by which maternal experience can affect the fetus (Gitau, Cameron, Fisk, & Glover, 1998; Monk et al., 2000; Teixeira, Fisk, & Glover, 1999).

During recent years, researchers have shown a strong interest in the effect of the fetal environment during pregnancy on both the child and the grown adult (Barker, 1992; Bateson 2001).[3] For example, ultrasound studies have shown that fetal behaviour can be affected by maternal anxiety (Groome, Swiber, Bentz, Holland, & Atterbury, 1999). It is well documented that a pregnant woman's experience of severe distress and anxiety can have adverse effects on the pregnancy and the unborn child (Catalano & Hartig, 2001; Glover, Teixeira, Gitau, & Fisk, 1999; Hedegaard, Henriksen, Secher, Hatch, & Sabroe, 1996; Lou et al., 1994; Seng et al., 2001). Two recent studies document a statistical association between strong maternal emotional distress in the first trimester of pregnancy and certain fetal malformations (Carmichael & Shaw, 2000; Hansen, Lou, & Olsen, 2000), and there appears to be a link between maternal anxiety and reduced fetal cerebral circulation (Sjöström, Valentin, Thelin, & Marsal, 1997; Teixeira et al., 1999). In addition, maternal anxiety related to pregnancy has been associated with behavioural problems in early childhood (O'Connor, Heron, Golding, Beveridge, & Glover, 2002).

It is known that a prenatal screening test result that indicates a risk of fetal abnormality can induce clinically significant anxiety and distress in many expectant women (Marteau et al., 1992; Roelofsen et al.[76], 1993; Santalahti et al., 1996). The question whether emotional distress arising in the wake of prenatal ultrasound screening can harm the fetus remains unanswered. We do not know how the mother's subjective state after disclosure of a soft marker relates to the child's health and well being. Because mothers may experience a variety of psycho-physiological states there may be different effects on the unborn child.

The dominant tradition of bioethical reasoning, with its origins in the principle-based approach of Beachamp and Childress (1994), does not easily accommodate the maternal–fetal symbiosis (Alderson, 2001; Donchin, 2001; Petchesky, 1994). Pregnant woman and fetus are thus discussed as separate entities, one contained within the other. Authorities within obstetrical ethics refer to 'the fetus as a patient' (Chervenak & McCullough, 1996, 1999), the 'patient within the patient', or even 'the target' of investigation (Blaas, 1999). This rupture of the fetal–maternal unity can be interpreted as a consequence of ethical reasoning being initially informed by a discourse concerning *unwanted* pregnancies and non-selective abortions. Analysis related to abortion logically regards maternal and fetal rights as separate from each other as it conceptualises the embryo as maturing from a person-to-be to a viable individual with a certain, yet limited, consciousness and a future potential for rationality. We believe there is a strong argument for discussing *the wanted pregnancy* (or any pregnancy destined to continue) in terms of *one existential nucleus*—the most basic, developmentally dynamic and vulnerable of all human relations.

Conclusions

The most fundamental principle of biomedical ethics is non nocere, not to harm. Yet, an analysis of the

[3] See also the special issue of International Journal of Epidemiology 30(1) (2001) titled Fetal origins of health and disease.

published biomedical literature makes evident that the practice of routine fetal screening by obstetrical ultrasound applying the latest in diagnostic equipment has caused harm to an unknown number of expectant parents and unborn children during the last decade. This has resulted from the fact that many ultrasound examiners have counselled pregnant women about an increased risk for fetal chromosomal aberrations on the basis of subtle findings in the ultrasonographic image, interpretations that have proved to be misleading as solid scientific evidence on the significance of the findings accumulated at a later date. Profound and private moral dilemmas arise as a direct consequence of premature application of an advancing medical technology in a routine clinical setting.

A second conclusion of this paper is that the implementation of ever-advancing biotechnology has placed clinicians in obstetrics and prenatalogy in an arena where medicine, social values and culturally determined meaning are closely intertwined. In that context, expert examiners have found themselves presenting unprecedented ethical dilemmas to parents-to-be, dilemmas which involve diagnostic options that endanger the lives of normal children-to-be.

Finally, the present analysis documents how technical advances related to imaging technology have come to challenge the biomedical tradition of considering scientific knowledge production as a value neutral act per se. By the same token, our concept of the fetal–maternal relationship, which has until now been conceptualised as either biologically or juridically determined, has also been challenged. The recently emerging side-effects of fetal ultrasound screening shed new light on the maternal–fetal unity and remind us that this unity has yet to be explored to its profound emotional and existential depths.

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PAPER II

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healthsciences

A matter of heart: the general practitioner consultation in an evidence-based world

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This article is based on a keynote presentation at the 12th Nordic Congress in General Practice in Trondheim, Norway in September 2002. The aim was to demonstrate the strengths and limitations of evidence-based medicine (EBM) in a primary healthcare setting. The presentation comprised two separate lectures discussing an authentic case history from everyday practice that had been presented to the authors by the congress organisers. Initially, Peter Nilsson overviews the correct approach to the situation as described according to EBM. Subsequently, Linn Getz questions whether we can be sure that application of EBM is necessarily in this particular patient's best interests. The title of the presentation, 'A matter of heart', has a double meaning. On the one hand it indicates an update on preventive cardiology, on the other it addresses the importance of academic courage (coeur = heart) among members of the medical community. The general practitioner is in a unique position to observe the interaction between the scientific paradigm of biomedicine and individuals, whether suffering from ill health or considering themselves healthy. It is our privilege and professional duty to reflect upon clinical experience and be open to critical debate.

Key words: **general practice, evidence-based medicine, unrecognised myocardial infarction, human sciences, ethics, concept of risk, risk perception, emotional health.**

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CASE HISTORY

The patient is a 70-year-old healthy male who, because of his age, needs a health certificate in order to have his driving licence renewed. He thus comes to see his general practitioner for the first time since he enlisted at the practice 8 years previously. He informs the doctor that he is healthy and emphasises the fact that he has always been healthy. Clinical examination reveals no sign of pathology, except for his heartbeat appearing somewhat irregular. The doctor thus orders an electrocardiogram (ECG), which shows no pathological arrhythmia. However, there is indication of an old coronary infarction in the ECG.

The doctor hesitates. She recognises that being 'of strong health' may be important to this man's identity. On the other hand, several scientific studies indicate that, compared to the general population, he is at increased risk of future coronary events. Furthermore, it is a medical duty not to withhold diagnostic information from patients. Choosing her words carefully, so as not to upset him, the doctor informs the man about the finding in the ECG. She asks him to make a new appointment so that his condition can be evaluated further. She then completes the certificate confirming that she considers him medically fit to drive a car and hands it over with a smile. She tells the man not to worry about his heart. The patient nevertheless appears hesitant and troubled as he leaves her office.

Despite having performed her task according to existing medical guidelines, the doctor is left with a feeling of unease, as if she has made a mistake.

Evidence-based medicine – the narrow road

PETER M. NILSSON

Why is evidence-based medicine (EBM) a narrow road? Even though we try to apply EBM in our daily clinical practice, we have to admit that the findings are generally based on randomised controlled trials (RCTs) and mean effects on a group basis (1). Any conclusions must therefore be translated to the individual level relative to age, gender, ethnic background and other relevant medical problems of the patient involved. Furthermore, EBM is often difficult to remember in all its aspects and it changes in focus and content. We therefore need continuous medical education as well as technical support through reliable information systems, e.g. easy computer access to MEDLINE/Pubmed and other relevant databases in the clinical office. Even if there are many inherent problems and shortcomings with EBM, it is a lifeboat

on a stormy sea of medical problems and ignorance, but it does not always reach harbour, for example when the patient suffers a morbid event or dies in spite of all good intentions and efforts.

Is a silent myocardial infarction (MI) in a 70-year-old man something to bother about or not? According to observational epidemiological data from the Framingham study, based on 708 MI cases among 5127 participants, more than 25% were detected by annual ECG check-up only (2), and more than half of these were "silent", especially in women and elderly men. After a follow-up period, it was concluded that a silent MI implied a similar risk for cardiovascular complications as a clinical MI (2). The risk associated with a silent MI cannot therefore be ignored and should be categorised as a triggering event for starting secondary prevention of coronary heart disease (CHD).

Can the physician confirm a diagnosis of silent MI? The first step would be to compare an abnormal current ECG with previous ECGs, if possible, to prove changes. Other technical options, not all of them necessary or needed in every case, are the following: a myocardial scintigram for evaluation of myocardial damage; an echocardiography for evaluation of cardiac failure and decreased ejection fraction; or a bicycle ergonometry test for evaluation of coronary ischaemia. In addition to these investigations, the full cardiovascular risk factor profile should be evaluated, including family history, medical history, lifestyle, blood pressure and blood sampling (fasting lipids, glucose). Balanced advice for an improved lifestyle (stopping smoking, increasing physical activity, proper diet) could be offered to all patients regardless of how well proven the cardiac damage is or is not – this is a message for everyone!

The five cornerstones for EBM in the secondary prevention of CHD/MI are: (a) improved lifestyle, (b) lipid lowering by statin use (based on the trials 4S, HPS, CARE and LIPID) or fibrate use (VA-HIT trial), (c) ACE inhibition (HOPE trial), (d) beta-receptor blockers (several trials) and (e) low-dose aspirin (several trials). These interventions should be discussed with the patient, not forced upon him/her, and ranked according to cost of intervention (Table I). In the recent Heart Protection Study, which included 19,000 high-risk individuals, the relative risk reduction (RRR) of acute MI was 24% by added-on simvastatin treatment compared to placebo and was not dependent on baseline LDL-cholesterol level (3). If all EBM proven therapies in secondary prevention could be jointly and successfully applied, a much higher RRR could be expected, as high as 80% according to some authors (4).

What about numbers needed to treat (NNT) in secondary prevention? This should be based on data from trials. In the Scandinavian Simvastatin Survival Study (4S), risk reduction during the trial was related to the absolute risk at baseline. In the 4S, the RRRs were 38%, 39% and 42% in patients at low, medium and high baseline risk. The absolute risk reduction (ARR) varied between 8% and 16% according to risk category (5). This corresponds to NNT (1/ARR) of 6 (95% CI: 4–11) to 11 (7–25) and 13 (8–34) patients for 6 years in order to prevent one cardiovascular event (5).

Table I. Evidence-based medicine (EBM) measures in secondary prevention of coronary heart disease, stratified for cost of intervention.

Low-cost interventions
Smoking cessation
Physical training
Low-dose aspirin
Medium-cost interventions
Beta-receptor blocker therapy
ACE inhibitor (generics) therapy
Statin (generics) and fibrate therapy
High-cost interventions
ACE inhibitor (non-generic) therapy
Statin (non-generic) therapy
Revascularisation (CABG/PTCA) procedures

How can the quality of secondary prevention for CHD be improved? In Sweden, a national project for better quality in secondary prevention has been on-going for 6 years based on a joint collaboration between the Swedish Society for Cardiology, the Swedish Society for General Medicine and the Swedish Federation for Health Care Staff in Cardiology. One of the findings, based on data from almost 30,000 patient visits, is that gender-equal care has been established for secondary prevention, as mirrored by similar lipid levels and drug treatment profiles in male and female patients after 1 year of follow-up, post-MI or following a revascularisation procedure (6).

The well-proven facts of EBM in secondary prevention should be acknowledged and not ignored, otherwise the doctor runs the risk of working in an unprofessional, unethical and non-legal way, at least according to Swedish recommendations (7,8), and most importantly the Health Care Legislation Act from 1980. This Act states that the patient should have the right to an informed choice whenever possible. However, no prevention should be forced on the patient; the crucial point is that it takes information and mutual communication between the doctor and the patient to make real the goal of an informed choice. Otherwise the doctor is working in a God-like manner, prohibiting the patient, an adult person, from making use of the relevant medical information for a personal choice (9). Therefore, we should all reflect

Table II. Which kind of GP doctor are you? A personal test for self-reflection.

The sphinx-like GP – knows everything, but says nothing.
The God-like GP – knows everything, but says only partly and wants the patient to be obedient and thankful whatever is said and done.
The charlatan GP – knows little, says anything.
The anxious GP – says little, makes a referral to hospital.
The ultra-democratic GP – knows something, asks the patient and relatives for a joint majority decision on what to do.
The "normal" GP – knows something, tries to balance evidence-based medicine with narrative medicine = consultation skills.

upon the kind of doctor/GP we would like to be – in our own view and in the eyes of the patient (Table II).

In conclusion, the EBM-believing physician should consider the absolute (total) risk of a cardiovascular event in the next 10-year period, and base treatment recommendations on this estimation according to current European (10) and national recommendations. In the case history presented here, all relevant risk factors should be evaluated and discussed for possible treatment. The patient should be an active partner in this process, and relevant information should be available from the physician or from recommended literature. If the patient in the end declares that he or she will not take medication, this is based on an informed choice and should be respected. To put it in another way: when mother EBM meets father narrative medicine (11–13), the two happy parents (14) will have a beautiful child called consultation skills. No child can be born without the interaction of two parents – a simple fact of life!

What kind of evidence is relevant to clinical decision-making?

Linn Getz

Despite convincing evidence that men who have undergone a MI may benefit from secondary prevention, I am not fully convinced that the medical encounter described in this case was health-promoting. Consider the outcome of the consultation: the patient appears hesitant and troubled as he leaves the office. The doctor is left with a feeling of unease, as if she has made a mistake. Is something of clinical and scientific significance going on? I see crucial questions in relation to several topics. These include:

- the validity of EBM to this particular man
- the significant correlation between emotions and cardiovascular health
- the fact that general practitioners show limited concordance with clinical guidelines in the field of preventive medicine
- issues related to philosophy, theory of science and medical ethics.

Connecting these diverse issues together in one argument is tricky. Medical reasoning, the way we have been taught to understand the physical heart of a patient, is detached from the human sciences that enable us to analyse the person's life-world. If we intend to apply a truly scientific approach, the case should be evaluated at the crossroads between these approaches. Biomedicine's inability to explain the placebo effect, however, documents that the paradigm cannot encompass the fundamental fact that human experience of meaning has profound effects on the physical body (15).

Is biomedicine in accordance with common sense?
I have presented this case history to several scholars. It tends to evoke one of two distinct responses. To illustrate these, I present an authentic dialogue between an American professor of medicine and his wife, a researcher in ancient history. This short dialogue (Table III) highlights three key issues: firstly, we see that from a traditional biomedical standpoint there appears to be no doubt as to whether the medical professional is doing good by *transforming a healthy person into a patient*. Secondly, it illustrates a statement recently put forward by David Sackett in his paper "The arrogance of preventive medicine" (16). Sackett states that *preventive medicine displays all three elements of arrogance*; aggressive assertiveness, presumptuousness and use of forcible arguments. Thirdly, I choose to believe that the opinion of the historian-wife reflects her knowledge that in Antiquity medicine was intertwined with philosophy, *the two disciplines together serving a common aim – the relief of human suffering*.

How exact is the evidence?
Unrecognised MIs may be present in about 3.5% of 70-year-old men in the general population (17). Studies indicate that their prognosis does not differ significantly from that of patients with recognised infarctions (17–19). Evidence-based calculations of

Table III. Dialogue illustrating two typical but differing views of how to handle the case in question.

Accompanying wife/historian:
"Of course it is best **not** to tell the patient"
Professor of medicine:
"But, darling, it is a matter of **saving his life**!"
Wife:
"Oh…"

the potential benefits of therapy for a patient like our man come from a heterogeneous mixture of studies, mostly related to patients with symptomatic heart disease. There is reason to ask whether the term 'evidence-based' may give the pretence of high scientific certainty, which in fact does not apply in this particular case. Table IV presents some 'best estimates' of the prognosis (17–19) and potential theoretical benefits of intervention (20).

Deducing from the group to the particular

Let us presume that the estimates (Table IV) are indeed valid for a group of men like our man. We intend to inform him about his personal risks and the potential benefits of therapy. However, as we counsel him on the basis of group-based data, we in fact commit a logical error, according to scholars of the theory of science (21,22). We choose to ignore individual variation and diversity, crucial phenomena in human biology. It should not therefore come as a surprise when epidemiological studies confirm that "The prediction of coronary heart disease risk in individuals is an imprecise science" (23).

Dealing with the concept of risk

During recent decades, there has been a steadily increasing focus on *risk* in Western societies (24–27). Adoption of the risk concept as a basis for preventive medicine on a large scale has taken place without much analysis and debate (25). The goals of medicine have expanded from the curative to the preventive sphere, a development that carries fundamental philosophical and ethical implications (25,27). The process of critical reflection in relation to risk intervention is still in its early stages.

For once, there is a problem related to *the communication of risk and treatment effects* (28,29). Doctors and patients tend to make different therapeutic considerations, depending on the way risk estimates are presented, i.e. what statistical model is used (29,30). Our man may be greatly interested in achieving a 40% reduction in the relative risk for a disease event during the next year, but reluctant if told that it is 98% likely that therapy will not affect his prognosis during the next year. The underlying data are the same. When can we say that a person makes an autonomous, informed choice?

Another issue yet to be explored is *how people experience the state of being 'at-risk'* (24,25,31,32). A philosopher reminds us how knowledge about medical risk may connect directly to the depths of our existence; our mortality, vulnerability and dependence (Arne Johan Vetlesen, pers. comm., 2002). As professionals we need to consider how this particular man may feel about the information he receives. Does his perception of his body change? What does he do, or stop doing? What will he tell his wife? What will she think if one day he looks a bit tired?

There are relatively few empirical studies on human experience of being labelled as 'at risk'. The results are contradictory and reveal what appear to be several paradoxes. The professional's preconception is of course that information about risk will increase people's sense of control over their lives and ultimately their quality of life. However, studies indicate that knowledge about medical risk may come to echo in people's minds in daily life. Food may become connected to ambivalence and guilt, innocent bodily symptoms to anxiety. There are empirical data indicating that knowledge about risk may cast shadows of doubt and insecurity over people's lives. One individual who was diagnosed as 'at risk' as he participated in a population study on cardiovascular disease worded this experience: "the fear is always there with you" (32). Despite the absolute risk of disease being relatively low, people also report that if you don't truly believe the statistics relate to you personally, there is no motivation to comply. Consequently, prevention may become a question of "complying or dying" (32). Are we setting up an emotional trap? It is not easy to say; research shows that many people express satisfaction with screening programmes and gratitude for the "gift of knowing" (33).

Table IV. Some "best estimates" of medical risks and potential benefits of therapy for the man in the case story. Estimates of therapeutical benefit are based on a number of intervention studies (included 4S) indicating a potential for 30–40% relative risk reduction for each drug prescribed for secondary prevention after a myocardial infarction.

No intervention (natural prognosis): 96–97% of 70-year-old men like this man are likely to survive each of the years to come, i.e. mortality in this group is 3–4% per year or 30–40% in the next 10 years (17,18).
Intervention may statistically reduce the mortality in this group somewhere between 1.5% and 2.5% per year. The maximum estimate presumes intervention with 3 or 4 drugs according to EBM, and furthermore presupposes that each drug will subsequently contribute a 30–40% relative risk reduction in relation to fatal CV events. Additive effects of several drugs, however, have not been documented scientifically.
Number needed to treat (NNT): If you intensively treat 40–60 patients like this man for 1 year, you might prevent 1 man from dying a cardiovascular (CV) death. After 10 years of treatment, 1 CV death may have been prevented for every 4–6 men.
Impact of diagnosis and therapy on quality of life in a group of patients like this:
There appears to be very little applicable evidence.

Emotional well-being and cardiovascular health

There is much evidence that changes in emotional life may affect the cardiovascular disease process itself for better or for worse (34–36). Depression may be associated with a twofold to threefold increase of cardiovascular mortality (36,37). A sense of hopelessness, defined as feeling unable to reach one's goals in life, has been shown to be predictive of a threefold increase in the incidence of hypertension in the near future, as well as worsening of overall cardiovascular status (38,39). We have no direct evidence that emotional stress related to information about medical risk can aggravate the disease process itself, but such a link appears biologically plausible.

The man in our case told his doctor that he considered himself "a man of strong health". However, subjective experience of this kind is not considered worthy of inclusion in cardiovascular risk estimates. There is much *evidence that a subjective perception of good health is a strong predictor of survival* (40–42). Our particular man may have a considerably better prognosis than estimated by so-called EBM.

Biomedical data – the ultimate truth?

The doctor in our case hesitates for a moment before allowing a diagnostic test result to overrule our man's subjective experience of being "a man of strong health". Her feeling of unease reflects an ethical dilemma necessary to discuss. The biomedical approach to the human being rests on systematic separations between 'normal' and 'deviant' findings, based on definitions made by the healthcare system itself. As medical professionals, we have a moral obligation "to tell the truth" to our patients. By tradition, the results of medical diagnostic tests have come to represent *ultimate truths* about the human condition, and thus something to be communicated irrespective of the context in which the results arise. In his 1973 analysis of the history of medical perception, social philosopher Michel Foucault describes the historical context in which *the clinical gaze* evolved, and how this gaze came to represent "a separating agent of truths" (43). As diagnostic technology becomes ever more widespread and refined, the professional's dilemma of having to communicate medical 'truths', despite considerable scientific uncertainty about their significance for the particular individual involved, appears to arise ever more frequently (44,45).

Limited concordance with clinical guidelines – what lies beneath?

Several studies indicate that general practitioners show limited adherence to clinical guidelines (46,47). Organ experts tend to indicate that the reason may be either ignorance or paternalism among GPs and consider it a violation of patient autonomy not to offer state-of-the-art medical intervention. In discussions of the present case, the question of autonomy typically arises at the final stage of the consultation, to emphasise the patient's democratic right to consider further diagnosis and therapy. But at that point a violation of our patient's autonomy has already taken place: our man never asked for a cardiovascular risk evaluation, his interest was driving his car. What is medical paternalism if not the use of medical technology in a somewhat arbitrary fashion on a healthy individual who is not asking for medical advice? Being aware of the scientific uncertainties outlined above *we cannot know that we are not doing more harm than good by imposing information about risk on this particular man*. Remember the prime principle of medical ethics – primum non nocere (first of all, do no harm) (9).

Whether analysing the case history from a biomedical or a humanistic perspective, the doctor in our case may find considerable theoretical and empirical support for her feeling of unease. Can it thus be that among general practitioners who show limited adherence to medical guidelines in the preventive sphere, there are doctors who actually show respect for a 'scientific truth' about their patient's condition that penetrates deeper than EBM (48)?

Humane doctoring

The medical practitioner who strives to combine biomedical evidence derived from group data (EBM) with a humanistic approach to the particular individual can be designated a *humane* doctor. Humane doctors hesitate *before* applying ECG electrodes to the chest of elderly gentlemen of very strong health. This is due not to ignorance in relation to medical guidelines (humane doctors do not hesitate to perform literature searches), but because a humane doctor acknowledges that the biomedical paradigm has fundamental shortcomings when it comes to explaining human health and suffering (49). With reference to the literature on empowerment and health, a humane doctor might deliberately choose to exclude the measurement of body mass index (BMI) in an overweight patient, despite this being part of a state-of-the-art risk evaluation. Making a point of excess body fat may sometimes be counterproductive to the symmetrical dialogue about health resources and future possibilities (50) which may facilitate constructive and lasting changes in a person's life.

Being a professional is not simply a question of commanding the various tools of medicine, such as medical guidelines. A medical professional also acknowledges that the use of reductionist medical tech-

nology may carry unintended side effects (22,44,45), and thus makes sure that its application is truly warranted in the first place. The decision of when to perform a diagnostic test and when to refrain from testing has to rest on scientific considerations that transcend the biomedical paradigm. As pointed out by Haynes, EBM does not make clinical decisions. People do (48).

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PAPER III

Education and debate

Is opportunistic disease prevention in the consultation ethically justifiable?

Linn Getz, Johann A Sigurdsson, Irene Hetlevik

Medical resources are increasingly shifting from making patients better to preventing them from becoming ill. Genetic testing is likely to extend the list of conditions that can be screened for. Is it time to stop and consider whom we screen and how we approach it?

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Most medical experts and health authorities consider consultations in primary health care ideal for opportunistic health promotion and disease prevention. Doctors are thus expected to discuss preventive measures even when they are not among the reasons for contact. But are such opportunistic initiatives ethically justifiable in contemporary Western medicine? We argue that doctors should maintain a clear focus on each patient's reasons for seeking help rather than be distracted by an increasing list of standardised preventive measures with unpredictable relevance to the individual.

Aims of a good consultation

The cornerstone of medical practice is the consultation between a patient who seeks help and a doctor whom the person trusts.[1] Several theoretical models have been developed to analyse and improve the quality of the consultation. In 1979, Stott and Davis presented an influential model that elicited four potentials of the encounter between patient and doctor: management of presenting problems, modification of help seeking behaviour, management of continuing problems, and opportunistic health promotion.[2] Since then, opportunistic preventive initiatives have become considered to be part of good medical practice.

From a moral point of view, preventive medicine—that is, initiatives to improve health among people who are currently free of symptoms—is fundamentally different from curative medicine, which is offered to patients who seek medical help. The two disciplines imply different promises and have different obligations to the individuals whose lives they modify.[3]

SUE SHARPLES

Expanding agenda of risk and prevention

When Stott and Davis developed their model, the number of relevant opportunistic initiatives was limited and seemed both technically feasible and ethically justifiable. However, interest in risk factors in healthy populations has expanded rapidly over the past two decades. A "risk epidemic" has occurred in medical publishing,[4] and the range of tests that can be done or started in general practice has become extensive. Discussion of lifestyle and monitoring blood pressure of healthy people are well established. Other indicators of cardiovascular risk have been added more recently, including blood lipid concentrations, body mass index, blood glucose concentration, and waist-hip ratio. As authoritative researchers advocate lower thresholds for intervention,[5 6] asymptomatic people are more likely to be labelled as at risk and needing medical intervention and follow up.

The box gives the most common conditions for which screening is encouraged in primary care. Genetic tests that may help predict some common diseases are likely to be included in the preventive armamentarium before long. To maintain control of the extensive preventive agenda, doctors are advised to "build into their practice a system of reminders and performance feedback to ensure necessary care."[7]

The expansion of preventive biomedicine has partly resulted from medical experts and other stakeholders using aggressively assertive and presumptuous arguments.[3] It is difficult to challenge the benevolent mission of a preventive programme, and

public health authorities have often welcomed such initiatives with more enthusiasm than has been warranted on scientific grounds.

Clinical inertia

In practice, doctors don't always follow clinical guidelines.[7–10] This phenomenon has been designated clinical inertia[7] and is generally interpreted as a sign of low quality care. Explanations include doctors overestimating the quality of the care they actually provide, lack of training, and use of soft excuses to avoid intervention.[7] Lack of time is also a well known explanation. The preventive measures discussed here are rarely effective enough to shift a large load of work away from treatment of manifest disease in the practice population. The total number of consultations will thus increase with the introduction of each new screening routine. A recent estimate shows that 7.4 hours of the working day of an average primary care physician in the United States would be needed to provide all services recommended by the US Preventive Services Task Force.[10]

Problems of opportunistic screening

Other important but more subtle factors may also contribute to doctors' limited compliance with guidelines on prevention. A clinician may hesitate to implement preventive guidelines because of the challenges of communicating risk.[11] Most specialists in preventive medicine show limited interest in the downsides of preventive programmes and early intervention.[3 12] The individual's decision about whether to participate should, however, not be regarded as trivial.[12] The professional who offers a test carries a considerable responsibility because informed consent presupposes an understanding of the limitations of the programme.[13] Every test carries a chance of misclassification of disease and false positive test results that lead to further interventions that do not benefit the patient and may cause harm.[12 14] In addition, negative results can give false reassurance.

Furthermore, patients and doctors tend to make different choices depending on the way statistical estimates of potential medical benefit are presented.[11 12 15] A 55 year old man may, for instance, be quite interested in an 18% reduction in the relative risk of dying from colorectal cancer but more reluctant if told that screening implies an absolute risk reduction of only 0.014% a year. He might alternatively consider that the likelihood of not dying from colorectal cancer is 99.34% if you are screened and 99.20% if you are not screened (numbers based on data in Kronborg et al[16]). Unless the doctor is willing to solve this information dilemma by using a simple paternalistic reminder such as, "take the test, it is good for you," many preventive interventions seem too complex to suit Stott and Davis's "window of opportunity."[2]

Another factor affecting clinical inertia may be the applicability of research. Doctors who keep abreast of scientific publishing are likely to become nihilistic when reading that interventions which are effective in optimal settings may be of marginal benefit in everyday practice or even do more harm than good.[17–19] Implementation of preventive medical measures on a large scale is thus not only becoming technically unmanageable, but a matter of increasing ethical concern in relation to individual patients.[19]

A final, decisive factor contributing to clinical inertia may be the professional insight that health is affected by factors other than those included in evidence based biomedicine.[1 20–23] Measurable pathophysiological disturbances should not necessarily be interpreted as the ultimate cause(s) of disease and suffering. External factors, such as social inequality and destructive human relations, greatly influence health and disease.[1 21 23] A focus on biotechnological interventions may divert the dialogue between patient and doctor away from important social and relational issues relevant to health.[1 21] It is not necessarily good medicine to focus on the management of bodily risk factors in individuals who ask for help to take control of their lives.

Conditions screened for in primary care

Hypertension
Coronary heart disease
Obesity
Hypercholesterolaemia
Diabetes
Breast cancer
Colorectal cancer
Cervical cancer
Chlamydia
Osteoporosis
Depression
Dementia
Alcohol misuse

Patient autonomy in preventive medicine

The fall in professional autonomy and power of individual doctors over the past few decades might be expected to have resulted in increased patient autonomy. The ongoing increase in centralised surveillance and corporate power[24 25] may, however, unintentionally compromise patient autonomy and quality of preventive care. As the list of accessible preventive tests lengthens and thresholds for intervention are lowered, a doctor who adheres to all recommendations for provision of preventive services may ultimately be able to find something abnormal in everybody.

Relatively few empirical studies have examined the effect of being labelled at risk. The results are contradictory. The professional's preconception is, of course, that information about risk will increase people's sense of control over their lives and ultimately their quality of life. But there is also a potential for risk information to cast shadows of doubt and insecurity over people's lives, which means it may undermine their experience of integrity and health.[8 20]

The concept of patient autonomy should be re-examined in light of the rapid expansion of preventive biomedicine.[19 26] It obviously embraces a person's freedom to consider, choose, or reject preventive or therapeutic options after receiving sufficient information. Once information about medical risk has been passed on to a person, however, it cannot be retracted. Respect for autonomy should therefore also honour the person's right not to be opportunistically confronted with knowledge about biomedical risks that are unrelated to his or her reasons for seeing the doctor.[20]

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Summary points

Opportunistic disease prevention and health promotion are regarded as part of good primary health care

The number of relevant preventive measures has increased greatly over the past two decades

Decisions about preventive measures need proper discussion about both benefits and harms, which takes time

An extensive preventive agenda may divert the dialogue between patient and doctor away from important social and relational issues relevant to the patient's health

Routine opportunistic preventive initiatives may no longer be ethically justifiable in contemporary Western medicine

Future consultations

Clinical inertia in implementation of preventive medical guidelines should not necessarily be taken as a sign of low quality care. It is time to reconsider the extent to which specific, opportunistic initiatives to prevent disease among asymptomatic individuals should remain a core element of everyday consultations in Western medicine. It is certainly good medical practice to identify, emphasise, and support health promoting resources,[27] skills, and activities that have a logical link to the patient's reason for coming to see the doctor. Other opportunistic initiatives may also seem appropriate. Doctors could increase patient autonomy by inviting the patient to introduce a topic rather than using a computerised reminding system. An open ended invitation may be one way to proceed. For example, "It could be that you have been considering other things that might be good for your health? If there is something you would like to discuss, you are welcome."

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Corrections and clarifications

Why do children have chronic abdominal pain, and what happens to them when they grow up? Population based cohort study
An error we made five years ago has just surfaced. In this article by Matthew Hotopf and colleagues (*BMJ* 1998;316:1196-2000), we got a number wrong in the Results section. The final sentence of the first paragraph should start: "Of the risk set, 52 [not 32] were followed up to the age of 36 years."

Sexual health
We muddled the start of the "services" section of the summary box in this editorial by Michael Adler (12 July, pp 62-3). The first two bullet points should have been combined and have read: "Urgent review of staffing requirements and an increase in the number of consultant posts."

Rhabdomyolysis
In converting to *BMJ* style the widely used term "9/11" in this editorial by Russell Lane and Malcolm Phillips (19 July, pp 115-6), we inadvertently referred to the attacks on the World Trade Center in New York as taking place on 9 September 2001. The attacks took place, as we all know, on 11 September.

PAPER IV

ORIGINAL PAPER

Taylor & Francis
healthsciences

Ethical dilemmas arising from implementation of the European guidelines on cardiovascular disease prevention in clinical practice

A descriptive epidemiological study

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Objective **– Our first objective is to describe total, age- and gender-specific prevalences of subjects in a well-defined population for whom medical follow-up is indicated due to unfavourably high blood pressure and/or cholesterol levels, as defined by the 2003 European guidelines on cardiovascular disease prevention in clinical practice. Our second objective is to highlight scientific questions and ethical dilemmas relating to implementation of the guidelines.**

Design, setting, and participants **– Cross-sectional population study comprising 62 104 adult Norwegians aged 20–79 years who participated in The Nord-Tröndelag Health Study 1995–97.**

Main outcome measures **– Total, age- and gender-specific point prevalences of individuals with total cholesterol ≥5 mmol/l and/or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or taking antihypertensive medication.**

Main results **– In total, 76% of individuals aged 20–79 years have an "unfavourable" cardiovascular disease risk profile, according to guideline definitions. The point prevalence of individuals with cholesterol and/or blood pressure above the recommended cut-off points increases with age. By age 24, the prevalence reaches 50%. By age 49, it reaches 90%. Men below 50 years of age have higher combined risk prevalence than women.**

Conclusions and implications **– Implementation of the 2003 European guidelines on CVD prevention would label a large majority of Norwegian adults as having unfavourably high cholesterol and/or blood pressure levels. The current biomedical standards appear to invalidate demographic health statistics. The theoretical basis on which the guidelines rest should thereby be scrutinized with regard to scientific methodology and consistency. Important ethical dilemmas arise at the point of guideline implementation, relating to risk labelling and medicalization, as well as resource allocation and sustainability within the healthcare system.**

Key words: **cardiovascular disease, clinical guidelines, ethics, general practice, preventive medicine, risk, sustainability.**

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Clinicians are expected to implement clinical guidelines such as the 2003 European guidelines on cardiovascular disease (CVD) prevention in their everyday practice. There has, however, been little debate about the pragmatic and ethical aspects of guideline implementation within the biomedical community.

- Implementation of the 2003 European guidelines on CVD prevention would label 76% of Norwegian adults 20 years and older, and 90% of individuals 50 years and older, as having unfavourably high cholesterol and/or blood pressure levels.
- We see important ethical dilemmas arising at the point of guideline implementation, relating to medicalization, resource allocation, and sustainability within the healthcare system.

Identification of risk factors for future disease and efforts to modify risk among currently asymptomatic individuals have expanded rapidly over the past decades (1,2). This is particularly true in relation to risk factors associated with cardiovascular disease (CVD) (2,3).

Serum cholesterol and blood pressure (BP) are continuous variables. More or less arbitrarily chosen cut-off points have been defined to identify individuals with the highest disease risk (2). Since authoritative guidelines on the management of hypertension were issued in 1962 (4), subsequent versions of guidelines for BP and blood lipid control have presented ever lower cut-off points for intervention (2). Every decrease of level seems to have been legitimized as a

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contribution to increased safety and health in the population. However, the rationale of applying risk factor thresholds in clinical decision-making is currently under scrutiny (5).

The latest version of the European guidelines on CVD prevention in clinical practice was published in 2003 (6). The authors state that the aim of presenting guidelines is to "present all the relevant evidence" to facilitate clinical decision-making. The guidelines "should be considered as the framework in which all necessary adaptation can be made in order to reflect different political, economic, social and medical circumstances" (6).

According to the guidelines, total serum cholesterol should be below 5 mmol/l in general, and lifestyle advice and medical follow-up are recommended for individuals with cholesterol equal to or above this level. Likewise, the guidelines recommend counselling and medical follow-up for persons with systolic BP $\geq$140 mmHg, and/or diastolic BP $\geq$90 mmHg.

Clinical guidelines represent consensual expert recommendations derived from population-based data and are meant to facilitate decision-making among clinicians with regard to individual patients. Ample population-based data on the distribution of CVD risk factors across Europe are available (7). However, surprisingly few researchers have highlighted the theoretical, methodological, pragmatic, and ethical aspects that are aggregated in the task of implementing guideline recommendations throughout a given population (8–10). To our knowledge, no attempts have been made to address these questions with regard to the current European guidelines on CVD prevention in clinical practice (6). The first objective of this study is to describe the total, age- and gender-specific prevalences of subjects in a well-defined population for whom medical follow-up is indicated due to unfavourably high BP and/or cholesterol levels, as defined by the guidelines. The second objective is to highlight scientific questions and ethical dilemmas relating to implementation of the guidelines.

Table I. Participants, means and standard deviations ($\pm$SD) of arterial blood pressure (BP, mmHg), body mass index (BMI, kg/m^2) and serum cholesterol (mmol/l), and prevalence of smokers among males and females in the Norwegian Nord-Tröndelag Health Study 1995–97 (HUNT 2).

Age groups	Participants	Systolic BP[1]	Diastolic BP[1]	BMI[2]	Cholesterol[3]	Smokers[4] %
Males						
20–24	1761	132.4±12.4	70.4±9.0	24.6±3.5	4.6±0.9	26.5
25–29	2163	132.8±11.9	73.8±8.8	25.5±3.4	5.0±1.0	27.6
30–34	2579	132.5±12.4	76.1±9.2	26.1±3.5	5.3±1.0	28.6
35–39	2820	132.5±12.9	78.3±9.4	26.3±3.3	5.6±1.1	30.4
40–44	3161	133.6±13.6	81.4±9.8	26.4±3.3	5.9±1.1	35.4
45–49	3334	136.0±15.3	84.1±10.5	26.8±3.3	6.0±1.1	36.6
50–54	3064	139.3±17.2	86.2±10.8	27.1±3.5	6.1±1.1	34.4
55–59	2333	142.5±18.8	86.0±10.9	26.9±3.4	6.2±1.1	32.8
60–64	2113	146.1±20.7	86.9±11.6	27.1±3.4	6.2±1.1	32.5
65–69	2232	150.5±22.2	86.8±12.5	26.9±3.6	6.2±1.1	35.4
70–74	2134	152.0±22.1	85.8±12.4	26.7±3.6	6.2±1.1	32.7
75–79	1594	154.6±23.2	85.3±13.0	26.7±3.5	6.1±1.2	27.4
Total	29 288					
Missing: [1]103; [2]158; [3]86; [4]3008						
Females						
20–24	2156	121.3±11.3	69.8±8.3	24.3±4.1	4.8±1.0	29.1
25–29	2561	120.0±11.6	70.8±8.6	24.9±4.5	5.0±1.0	32.8
30–34	2917	120.0±12.2	72.1±9.0	25.1±4.3	5.1±1.0	36.1
35–39	3207	121.4±13.1	74.3±9.5	25.2±4.2	5.2±1.0	40.4
40–44	3478	125.3±15.2	77.0±10.0	25.4±4.1	5.5±1.0	44.1
45–49	3566	129.9±17.5	79.1±10.8	26.1±4.3	5.8±1.0	43.3
50–54	3314	135.7±19.5	81.6±11.2	26.8±4.6	6.2±1.1	37.7
55–59	2461	140.2±20.2	82.4±11.4	27.0±4.4	6.6±1.2	35.7
60–64	2292	146.1±22.1	83.1±11.8	27.6±4.8	6.8±1.2	32.9
65–69	2418	152.2±22.7	84.3±12.5	27.7±4.6	6.9±1.2	31.2
70–74	2382	157.3±23.3	84.7±13.6	27.8±4.7	6.9±1.3	21.5
75–79	2064	161.8±24.1	85.1±14.3	27.9±4.7	6.9±1.3	13.2
Total	32816					
Missing: [1]103; [2]297; [3]89; [4]4852						

STUDY POPULATION AND METHODS

The present data are derived from a large and well-organized Norwegian population study, "The Nord-Tröndelag Health Study 1995–97 (HUNT 2)" (11). The HUNT 2 study was designed to investigate the significance of biomedical risk factors. Its design and methods have been described in detail elsewhere (11). The overall participation rate in the HUNT 2 study was 76% among women and 67% among men (both sexes combined 20–29 years: 49%; 30–39 years: 68%; 40–49 years: 77%; 50–59 years: 81%; 60–69 years: 86%; 70–79 years: 80%). The present study is based on data from all participants aged 20–79 years, in total 62 104 individuals (29 288 males and 32 816 females) (Table I). The HUNT 2 population can be considered representative of the total Norwegian population regarding demography, socioeconomic factors, morbidity and mortality (11).

In the HUNT 2 survey, BP was measured on persons in seated position by specially trained personnel using a Dinamap 845XT based on oscillometry. Cuff size was adjusted after measuring the arm circumference, and BP was recorded as the mean values of the second and third of three measurements performed consecutively at the same visit. Total cholesterol was measured by an enzymatic colorimetric cholesterolesterase method (11). In the present analysis, unfavourably high BP is defined as systolic blood pressure $\geq$140 mmHg and/or diastolic BP $\geq$90 mmHg, or that the person reported taking antihypertensive medication, regardless of the actual measures. The cut-off point for unfavourably high serum cholesterol is $\geq$5 mmol/l, in accordance with the guidelines (6).

The SPSS statistical package, version 12.0, was used for statistical frequency analyses. Age standardization weight for 20–79 years was performed using the World standard (7,12).

All surveys in HUNT 2 were approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research. The present analysis was approved by the steering committee of the HUNT Research Centre.

RESULTS

Table I gives data regarding the participants and selected variables underlying CVD risk estimates in the present study. The point prevalence of individuals with serum cholesterol and/or blood pressure levels above the recommended cut-off points increases with age (Fig. 1), reaching 50% (95% confidence interval (CI) 47.2–53.7) by age 24 years, and 90% (95% CI 88.4–91.5) by age 49 years. Age-standardized total prevalence of risk labelling among adults 20–79 years is 76% (95% CI 74.7–77.0). Men below 50 years of age have higher combined risk prevalence than women, whereas women aged 55 years or older have a slightly higher combined risk prevalence than men (Table II).

DISCUSSION

Implementation of the European guidelines on CVD prevention in clinical practice (6) will label three out of four Norwegian adults aged 20 years and older as in need of medical counselling and follow-up due to unfavourably high levels of cholesterol and/or blood pressure. This finding evokes fundamental scientific questions and, simultaneously, it depicts ethical dilemmas related to medicalization, resource allocation and sustainability that require an analysis in their own right (13,14).

The HUNT 2 study included a well-defined population with participation rates among the highest reported in large population studies (11). A comprehensive non-participation study after the HUNT 1 survey could not find evidence of a selection of health measures in the younger age groups where participation rate was lowest (11).

Together with the majority of the European countries, Norway is classified as a "high risk" region with regard to CVD (6). Compared with other European high-risk regions in the MONICA project (third phase, 1992–94) (7), the HUNT 2 population did not differ significantly in respect of cholesterol levels and smoking habits. Blood pressure levels were somewhat higher in the HUNT 2 population than in most comparable countries, but lower than in Finland. However, it is cholesterol levels and not BP alone that ultimately lead to the high prevalence of risk labelling (Table II).

Risk definitions – scientific and ethical dilemmas

Disease prevention and health promotion have been and will remain two central goals of medicine (14). Definition of relevant cut-off levels for individual risk intervention is, however, crucial, and the resulting preventive tasks should appear meaningful and manageable from the point of view of practising clinicians. Norway has one of the world's longest-living and healthy-living populations, according to WHO statistics (15). In such a context, health professionals might reasonably come to experience confusion and alienation when instructed to inform a large majority of people that their cardiovascular health is not "good enough" according to current

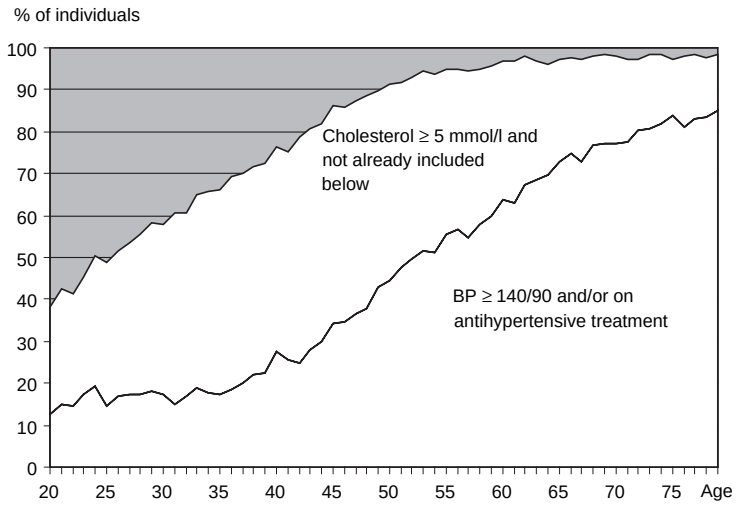

Fig. 1. Point prevalence of individuals 20–79 years (males and females combined) with unfavourably high blood pressure (BP) and/or cholesterol levels, as defined by the 2003 European guidelines on cardiovascular disease prevention in clinical practice.

biomedical standards (16). Failing adherence to clinical guidelines emerges as a logical and likely consequence (2).

Confusion due to flawed concepts or scientific incoherence?

Our analysis demonstrates that the scientifically grounded consent which is manifested in the recommendations of the current guidelines would reverse the biomedical distinction between norm and deviation, traditionally associated with health and sickness, to mean the opposite. In our study population, the "unhealthy" or "pathological" state would acquire the state of the norm, and the "healthy" or "normal" state would become the exception (Fig. 1). Such a paradoxical medical scenario could make sense if our study population was structurally disadvantaged by international comparison. A positive correlation has repeatedly been documented between unfavourable socioeconomic conditions and an increased risk of CVD (17,18). International health statistics do not, however, indicate that Norwegians are socioeconomically deprived or in a general health crisis (15). The "risk epidemic" among the HUNT 2 population should be thoroughly analysed in advance of biomedical interventions that involve a large majority of individuals.

Relation between disease prevention and health promotion

Current guidelines for prevention of CVD in clinical practice are based on the scientific presupposition that individual information regarding medical risk increases a person's autonomy and sense of control over her/his life (19). Activities aiming to prevent disease are thereby automatically considered to be health promoting. Identification of disease risk in clinical practice can in some instances incite favourable changes in people's health-related behaviour and medical prognosis. To what extent consultation-based lifestyle interventions can be expected to produce substantial behavioural changes however, is poorly documented (20). It is also possible that the medical act of disclosing inherent bodily vulnerabilities to an asymptomatic person can have negative consequences (19,21–24). Before embarking on the project of implementing the current guidelines in the general population, it is important to consider that risk intervention among asymptomatic individuals is an intellectually demanding, scientifically problematic, value-laden, and potentially harmful activity.

Dilemmas of risk discourse in the clinical encounter

It is inherently difficult to explain the methodological premises for the risk factor concept and the statistical calculations pertaining to a given risk measure in a meaningful way to a patient – even for a physician

Table II. Point prevalence (and 95% CI) of unfavourable blood pressure (BP) levels, cholesterol levels, and combination of these, as defined by the 2003 European guidelines on cardiovascular disease prevention in clinical practice, among the participants in the Norwegian Nord-Tröndelag Health Study 1995–97 (HUNT 2).

Age groups	BP ≥140/90 and/or on antihypertensive treatment % (95% CI)	Cholesterol ≥5 mmol/l % (95% CI)	Combined[1] % (95% CI)
Males			
20–24	27.3 (25.2–29.3)	31.1 (29.0–33.3)	46.9 (44.5–49.2)
25–29	28.8 (26.9–30.7)	48.7 (46.6–50.8)	60.3 (58.2–62.4)
30–34	27.5 (25.7–29.2)	62.6 (60.7–64.5)	71.4 (69.7–73.2)
35–39	29.8 (28.1–31.5)	73.3 (71.6–74.9)	78.8 (77.3–80.4)
40–44	35.2 (33.6–36.9)	80.0 (78.6–81.4)	84.9 (83.7–86.2)
45–49	44.4 (42.7–46.1)	84.9 (83.7–86.1)	90.4 (89.4–91.4)
50–54	54.5 (52.8–56.3)	87.6 (86.4–88.8)	93.3 (92.4–94.2)
55–59	60.2 (58.2–62.2)	87.8 (86.4–89.1)	93.7 (92.7–94.7)
60–64	68.7 (66.7–70.7)	88.4 (87.7–89.8)	95.7 (94.8–96.6)
65–69	74.6 (72.8–76.4)	87.8 (86.4–89.2)	96.9 (96.1–97.6)
70–74	77.1 (75.3–78.9)	87.7 (86.3–89.1)	96.5 (95.6–97.3)
75–79	79.2 (77.2–81.2)	85.9 (84.2–87.6)	96.2 (95.1–97.1)
Females			
20–24	6.7 (5.7–7.8)	38.9 (36.8–40.9)	42.1 (40.0–44.2)
25–29	6.8 (5.9–7.9)	46.0 (44.1–47.9)	48.4 (46.5–50.4)
30–34	8.2 (7.2–9.2)	51.7 (49.9–53.3)	54.3 (52.5–56.1)
35–39	11.7 (10.6–12.8)	59.1 (57.4–60.8)	62.2 (60.5–63.9)
40–44	19.7 (18.4–21.0)	68.9 (67.4–70.5)	73.1 (71.6–74.6)
45–49	30.7 (29.2–32.2)	80.2 (78.9–81.5)	85.1 (84.0–86.3)
50–54	43.3 (41.6–45.0)	88.4 (87.3–89.5)	92.3 (91.3–93.2)
55–59	53.8 (51.8–55.7)	92.7 (91.6–93.7)	96.1 (95.3–96.9)
60–64	64.5 (62.5–66.4)	95.3 (94.4–96.1)	97.9 (97.3–98.5)
65–69	75.1 (73.4–76.8)	94.9 (94.0–95.8)	98.5 (97.9–98.9)
70–74	81.8 (80.2–83.3)	95.9 (95.0–96.6)	99.2 (98.7–99.5)
75–79	86.3 (84.8–87.8)	95.2 (94.2–96.1)	99.3 (98.9–99.6)

[1]BP ≥140/90 and/or on antihypertensive treatment and/or cholesterol ≥5 mmol/l.

who is fairly familiar with this theoretical framework (19,21–24). Furthermore, evidence-based medicine (EBM) does not inform the clinician to what extent a recommended cut-off point represents a valid demarcation line in relation to each particular individual (21–26). The concept of EBM operates solely with rude mathematical abstractions of the human condition. It regards any given human being as a random representative for a roughly defined epidemiological group, and, as such, determinable by quantifiable measures. If regarded from the point of view of the humanistic sciences, however, a human being is above all a particular, subjective, moral, and interactive being. And it is well documented that a person's being-with and belonging-to relationships, replete with issues of power and resistance, are essential to health (19,27–29).

From abstract figure to personal experience

A biomedical cut-off point such as serum cholesterol 5.0 mmol/l is a methodological artefact (2,5). In the context of the particular consultation, however, a mathematical abstraction gains normative impact (30–33). Figures derived from "everybody – regardless of the circumstances" acquire the meaning of "me – here and now". The shortage of sound explorations of how medical communication carrying meanings such as "you have a somewhat increased risk of cardiovascular disease" affects people's understanding of themselves, their bodies, and their lives should engender professional concern (21). Medical risk discourse connects to the existential depths of human life and is a reminder of human vulnerability and mortality. There is some evidence that information about risk of future disease can cast shadows of doubt and insecurity over people's lives (21–24). In an unfavourable context, focus on disease risk may thereby undermine an individual's subjective experience of integrity, well-being and health (14,19,21). This fact should be considered in light of epidemiological studies showing that a person's subjective perception of being in good health is a strong predictor of survival (34). There are also clear links between emotional life and CVD development (35).

Evidence of efficacy of guided CVD prevention under controlled research circumstances implies no guarantee of effectiveness in everyday clinical practice (2,36). Nor does it allow any prediction of whether the intervention, if effective, is defensible, compared with use of resources for other health needs (2,36).

Adherence to guidelines revisited

Practising clinicians show limited adherence to clinical guidelines (2,37–39). This phenomenon has been termed "clinical inertia" (38), indicating what seems to be unacceptable professional ignorance or disobedience resulting in low-quality care. Several explanations for this phenomenon have been put forward; of particular interest for our discussion are: doctors overestimating the quality of the care they actually provide, lack of training, and use of "soft excuses" to avoid intervention (38). The present study allows us to differentiate and sophisticate this discussion. It indicates that limited concordance with clinical guidelines may, rather than revealing professional shortcomings, also represent a reasonable, professional decision not to overemphasize bodily risk factor monitoring at the cost of other topics with major relevance to people's health (19,21,37,39,40). The task of implementing the guidelines evokes fundamental questions in relation to prioritizing of time and resources (10) and sustainability of the healthcare system (14), even in Norway where access to healthcare is excellent by international comparison (15) and per capita expenditure on health is already among the highest in the world (15).

CONCLUSIONS AND IMPLICATIONS

Implementation of the current European guidelines for prevention of CVD in clinical practice in one of the world's longest-living and healthiest-living populations would lead to identification of an "unfavourable" CVD risk profile in three out of four adult Norwegians. By the rules of formal logic, the "healthy" state, traditionally considered to be the "normal" state, would thereby become the exception. This finding represents a quest to scrutinize the theoretical basis upon which the guidelines rest, with regard to methodology and scientific consistency. Simultaneously, important ethical dilemmas arise at the point of guideline implementation. In this paper we have focused primarily on issues related to medicalization and risk labelling of asymptomatic individuals. Our results, however, demonstrate the need for a comprehensive evaluation of the guidelines with regard to resource allocation and sustainability within the healthcare system.

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PAPER V

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Estimating the high risk group for cardiovascular disease in the Norwegian HUNT 2 population according to the 2003 European guidelines: modelling study

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Abstract

Objective To estimate the high risk group for cardiovascular disease in a well defined Norwegian population according to European guidelines and the systematic coronary risk evaluation system.
Design Modelling study.
Setting Nord-Tröndelag health study 1995-7 (HUNT 2), Norway.
Participants 5548 participants of the Nord-Tröndelag health study 1995-7, aged 40, 50, 55, 60, and 65.
Main outcome measures Distribution of risk categories for cardiovascular disease, with emphasis on the high risk group.
Main results At age 40, 22.5% (95% confidence interval 19.3% to 25.7%) of women and 85.9% (83.2% to 88.6%) of men were at high risk of cardiovascular disease. Corresponding numbers at age 50 were 39.5% (35.9% to 43.1%) and 88.7% (86.3% to 91.0%) and at age 65 were 84.0% (80.6% to 87.4%) and 91.6% (88.6% to 94.1%). At age 40, one out of 10 women and no men would be classified at low risk for cardiovascular disease.
Conclusion Implementation of the 2003 European guidelines on prevention of cardiovascular disease in clinical practice would classify most adult Norwegians at high risk for fatal cardiovascular disease.

Introduction

Mortality from cardiovascular disease has declined considerably in most European countries since the early 1970s.[1] Interventions to modify risk factors have long been shown to reduce mortality and morbidity from cardiovascular disease, in both people with previously unrecognised disease[2] and people with established disease.[3] Intervention in people at high risk is an accepted method for disease prevention. Since the first US Framingham model for predicting heart disease risk was published in 1991, it has become ever more widely recommended that doctors in primary care carry out risk assessment by combining several risk factors for cardiovascular disease using algorithms. Until recently most risk equations have been derived from the Framingham study, but these calculations tended to overestimate risk in the European context.[4] A new European risk scoring system for cardiovascular disease, based on the first phase of the systematic coronary risk evaluation (SCORE) project, was presented in 2003.[5] The system is based on a pooled dataset of cohort studies from 12 European countries, among these Norway, and offers a format for estimating fatal cardiovascular disease risk that is suitable for clinical practice.[5] The system is embedded in the current version of the European guidelines on prevention of cardiovascular disease, issued by the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice in 2003.[6] The authoring body consists of eight European and international medical societies and experts. The guidelines aim to present all relevant evidence to facilitate clinical decision making in the primary and secondary prevention of cardiovascular disease, which can be adapted to different political, economic, social, and medical circumstances.[6]

The legal status of clinical guidelines for the prevention of disease is not fully established,[6] but authoritative recommendations contribute to expert and opinion leaders' definition of what constitutes good medical practice. Several studies have, however, shown clinicians' limited adherence to medical guidelines for asymptomatic conditions.[6–9] This is the case even in high risk situations, such as patients with angina pectoris or diabetes mellitus.[8] This phenomenon, termed "clinical inertia," has been partly attributed to too much work, too little time, and "soft reasons to avoid intensification of therapy."[7]

Population based data on risk factors for cardiovascular disease are available for many European regions.[10] The 2003 European guidelines, however, provide no estimates of the aggregated workload associated with implementation of the recommendations. We recently showed that implementation would result in three out of four Norwegians aged 20 or older being classed as in need of counselling because of high cholesterol or blood pressure levels.[11]

We estimated the high risk group in the Norwegian population participating in the Nord-Tröndelag health study 1995-7 (HUNT 2),[12] according to the 2003 European guidelines on prevention of cardiovascular disease.

Materials and methods

The 2003 European guidelines tackle the prevention of atherosclerotic disease in general (coronary heart disease, peripheral artery disease, and cerebrovascular atherosclerotic disease). Risk is defined in terms of the absolute probability of developing a fatal cardiovascular event within 10 years, and the threshold for high risk is defined as ≥ 5%.[6] The guidelines [6] specify a list of biomedical conditions that classify people at high risk (see box). These people require maximal clinical attention, with no further estimation of risk.[6] In remaining asymptomatic, apparently healthy people, risk estimation and counselling should be guided by the total risk level, as estimated from a chart produced by the systematic coronary risk evaluation project.

The European guidelines' clinical priority list

The clinical priority list in the European guidelines on cardiovascular disease prevention in clinical practice (pocket version). Individuals who fulfill criteria 1 or 2, or both are defined as at high risk

Priorities of cardiovascular disease prevention in clinical practice
1) Patients with established coronary heart disease, peripheral artery disease and cerebrovascular atherosclerotic disease
2) Asymptomatic individuals who are at high risk of developing atherosclerotic cardiovascular disease because of:
 a) Multiple risk factors resulting in a 10 year risk of ≥5% now (or if extrapolated to age 60) for developing a fatal cardiovascular event
 b) Markedly raised levels of single risk factors: cholesterol ≥8 mmol/l (320 mg/dl), LDL cholesterol ≥6 mmol/l (240 mg/dl), blood pressure ≥180/110 mmHg
 c) Diabetes Type 2 and diabetes Type 1 with microalbuminuria
3) Close relatives (first degree relatives) of:
 a) Patients with early-onset atherosclerotic cardiovascular disease
 b) Asymptomatic individuals at particularly high risk
4) Other individuals met in connection with ordinary clinical practice

Source: De Backer et al [6]

The chart comprises a table of the parameters sex, smoking status, systolic blood pressure, total cholesterol (or ratio of total cholesterol to high density lipoprotein), and age (40, 50, 55, 60, and 65 years). Risk is estimated by rounding a person's age to the nearest one shown on the chart, their cholesterol level to the nearest whole unit, and their blood pressure to the nearest multiple of 20 mm Hg.[5] The guidelines specifically recommend extrapolation of the risk estimate to 60 years when counselling people in the younger age groups. We calculated risk distribution both with and without extrapolation to evaluate its effect on the high risk group.

The chart is designed in two versions, for use in high or low risk populations. As the guidelines state that Norway is a high risk region, we analysed data using the high risk chart.

The guidelines encourage people with increased risk for cardiovascular disease to change their lifestyle.[6] To facilitate communication of risk, a person's combined risk estimate is visualised by "traffic light" colours. High risk is illustrated by increasingly dark shades of red. Intermediate risk (2%-4% risk of a fatal event within 10 years) is illustrated by yellow-orange, and low risk (≤ 1%) by green.

The Nord-Tröndelag health study 1995-7

Our population data were derived from the Nord-Tröndelag health study 1995-7, a large Norwegian population study that was designed to investigate the importance of biomedical risk factors. Its design and methods are described elsewhere.[12] Data were obtained from 66 140 participants. The study population has been considered fairly representative of the Norwegian population for demography, socioeconomic factors, morbidity, and mortality.[12]

To apply the guidelines' recommendations as precisely as possible, we included in the present analysis only people of the ages shown in the chart. The analysis is based on participants from the Nord-Tröndelag health study aged 40, 50, 55, 60, and 65 years, totalling 5548 people (2841 women, 2707 men). These participants answered two questionnaires; one sent by post before screening and the other presented at screening. A range of health topics was covered.[12] Of relevance to our study were questions about cardiovascular disease, diabetes mellitus, and smoking habits. For our analysis we define smoking as daily consumption of cigarettes, cigars, or a pipe.

In the Nord-Tröndelag health study, blood pressure was measured in seated participants by specially trained staff using a Dinamap 845XT based on oscillometry.[12] In our analysis we record blood pressure as the mean values of the second and third of three measurements carried out consecutively at the same visit. Blood sampling was carried out whenever the participants attended—that is, in the non-fasting state. Fresh serum was analysed on a Hitachi 91 autoanalyser. Total cholesterol and high density lipoprotein cholesterol were measured by an enzymatic colorimetric cholesterolesterase method.[12] Height was measured to the nearest 1.0 cm and weight to the nearest 0.5 kg. Body mass index was calculated.

Projection of the guidelines to the study population

We established the proportion of participants at high risk of cardiovascular disease in a stepwise manner, in accordance with the guidelines. We calculated the age and sex specific proportions that should be assigned to the high risk category on the basis of criteria 1 and 2b-c of the priority list (see box). We used the chart to estimate risk in the remaining participants. As the chart does not give exact cut-off points for systolic blood pressure and total cholesterol, we applied the following limits: systolic blood pressure (mm Hg) ≤ 119, 120-139, 140-159, and 160-179; total cholesterol (mmol/l) ≤ 3.9, 4.0-4.9, 5.0-5.9, 6.0-6.9, and 7.0-7.9.

Overall, 283 women (10% of the total) and 186 men (6.9%) were unclassifiable according to the chart owing to missing data, mostly on smoking habits. We included all participants in the denominator when we determined the distribution of risk categories.

We adapted the priority list on the basis of the data from the Nord-Tröndelag health study. Under criterion 1 we included only participants with a history of myocardial infarction or stroke. We did not calculate low density lipoprotein, as application of the Friedewald formula is unreliable in non-fasting people. We included participants who reported receiving treatment for hypertension and all people with diabetes mellitus in the high risk category.

We display graphically the risk distribution for cardiovascular disease among the Nord-Tröndelag health study population in two versions; one based on extrapolation to age 60 as recommended in the guidelines, the other based on the participants' age. In doing so we applied the colour system, without differentiating between shades of the same colour. Shaded red indicates people who are defined as at high risk on the basis of criteria 1 and 2b-c. Unshaded red indicates high risk according to the chart (criterion 2a). We used SPSS version 12.0 to analyse frequencies.

Results

Table 1 gives an overview of participants from the Nord-Tröndelag health study included in the present analysis. The participation rate varied from 70% to 89%. Table 2 shows the proportion of people categorised as at high risk on the basis of noticeably raised levels of single risk factors (see box) and the distribution of the combined risk categories, according to the chart of the systematic coronary risk evaluation project.

If all recommendations including extrapolation of risk to 60 years are applied, 22.5% (95% confidence interval 19.3% to 25.7%) of women and 85.9% (83.2% to 88.6%) of men aged 40 are classified as at high risk for fatal cardiovascular disease (fig 1 and table 2). Only 8.5% (6.5% to 10.9%) of women and no men aged 40 are classified as at low risk. By age 50, the high risk group includes 39.5% (35.9% to 43.1%) of women and 88.7% (86.3% to 91.0%) of men and by age 65, 84.0% (80.6% to 87.4%) of women and 91.6% (88.6% to 94.1%) of men.

Table 1 Participation rates, means, and prevalence of relevant risk factors among participants in Nord-Tröndelag health study 1995-7 (HUNT 2), Norway. Values are percentages (numbers) unless stated otherwise

	40 years		50 years		55 years		60 years		65 years	
Variable	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**
No of participants (participation rate)	657 (80.8)	624 (69.6)	709 (84.1)	698 (76.0)	554 (85.9)	555 (79.9)	471 (88.9)	411 (80.4)	450 (85.1)	419 (81.7)
Mean (SD) systolic blood pressure	124.0 (14.5)	133.6 (13.1)	133.1 (19.1)	137.5 (16.9)	138.8 (19.8)	140.6 (17.9)	144.6 (21.1)	144.9 (20.6)	150.7 (23.5)	148.4 (20.4)
Mean (SD) diastolic blood pressure	76.1 (9.8)	80.8 (9.9)	80.8 (11.2)	85.4 (10.9)	82.8 (11.4)	85.4 (10.8)	82.9 (11.6)	87.0 (11.4)	84.5 (13.0)	86.2 (12.1)
Mean (SD) total cholesterol concentration	5.4 (1.0)	5.7 (1.1)	6.1 (1.1)	6.1 (1.1)	6.5 (1.2)	6.2 (1.2)	6.8 (1.3)	6.1 (1.1)	6.8 (1.2)	6.2 (1.1)
Mean (SD) body mass index	25.4 (4.1)	26.3 (3.4)	26.5 (4.4)	27.0 (3.4)	27.1 (4.4)	27.1 (3.5)	27.8 (5.0)	27.1 (3.3)	27.5 (4.7)	27.1 (3.3)
Smokers	46.1 (281/610)	34.8 (204/586)	38.9 (240/617)	34.1 (220/646)	33.7 (157/466)	32.9 (166/505)	32.5 (123/379)	32.7 (118/361)	32.8 (114/348)	33.9 (122/360)
Total cholesterol ≥5 mmol/l	65.7 (430/654)	76.4 (475/622)	86.7 (615/709)	86.2 (600/696)	91.7 (508/554)	88.6 (491/554)	94.1 (443/471)	86.6 (355/410)	95.3 (429/450)	86.9 (364/419)
Blood pressure ≥140/90 mm Hg and untreated	15.2 (102/657)	36.0 (224/623)	29.8 (211/709)	41.7 (290/696)	37.3 (206/552)	44.8 (248/554)	42.2 (198/469)	52.1 (214/411)	43.8 (196/448)	46.8 (195/417)
Angina without myocardial infarction	0.2 (1/657)	0.0 (0/624)	1.3 (9/708)	2.1 (15/698)	1.1 (6/549)	2.5 (14/553)	3.8 (18/469)	4.9 (20/411)	4.5 (20/447)	7.5 (31/414)
First degree relatives with myocardial infarction before age 60	15.8 (92/581)	20.7 (105/508)	20.6 (132/640)	17.9 (104/582)	21.8 (108/495)	18.5 (86/464)	19.4 (86/444)	17.7 (63/356)	17.8 (76/426)	18.8 (71/377)

Figure 2 shows the distribution of risk categories without extrapolation to age 60. Extrapolation explains 86.0% of the high risk group after evaluation using the chart among women aged 55. The values for men are 64.4% at age 50 and 18.7% at age 55.

Discussion

Implementation of the 2003 European guidelines on prevention of cardiovascular disease in a well defined Norwegian population would class four out of 10 women and nine out of 10 men aged

Table 2 Percentages (numbers) of women and men at high risk for cardiovascular disease according to criteria 1 and 2b-c in priority list (see box), distribution of combined risk categories for cardiovascular disease among remaining individuals according to systematic coronary risk evaluation (SCORE) chart

	40 years		50 years		55 years		60 years		65 years	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**
Priority list:										
Established myocardial infarction or stroke	0.3 (2/657)	0.3 (2/624)	1.4 (10/708)	4.3 (30/698)	1.6 (9/549)	8.2 (45/552)	2.6 (12/467)	9.7 (40/411)	5.9 (26/444)	12.8 (53/415)
Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg	0.5 (3/657)	0.5 (3/624)	2.4 (17/709)	2.1 (15/698)	4.7 (26/553)	2.9 (16/554)	7.2 (34/470)	7.3 (30/411)	14.0 (63/449)	6.2 (26/418)
Cholesterol ≥8 mmol/l	1.1 (7/654)	3.5 (22/622)	6.3 (45/709)	5.5 (38/696)	13.0 (72/554)	5.6 (31/554)	17.8 (84/471)	5.4 (22/410)	16.2 (73/450)	6.2 (26/419)
Diabetes	0.3 (2/657)	1.3 (8/616)	2.3 (16/708)	1.6 (11/696)	2.4 (13/551)	3.8 (21/552)	2.8 (13/468)	4.6 (19/410)	3.8 (17/446)	4.6 (19/415)
Receiving treatment for hypertension	1.8 (12/655)	1.8 (11/621)	8.1 (57/708)	9.3 (65/696)	14.3 (79/551)	14.4 (80/554)	16.8 (79/469)	17.3 (71/411)	28.3 (127/448)	26.9 (112/417)
Sum high risk*	3.8 (25/657)	7.2 (45/624)	17.8 (126/709)	19.5 (136/698)	29.2 (162/554)	26.7 (148/555)	36.7 (173/471)	33.8 (139/411)	51.1 (230/450)	43.4 (182/419)
SCORE chart for combined risk among remaining individuals with extrapolation†:										
Unclassifiable‡	7.0 (46)	6.4 (40)	10.7 (76)	6.6 (46)	11.7 (65)	5.8 (32)	11.9 (56)	8.0 (33)	8.9 (40)	8.4 (35)
High risk	18.7 (123)	78.7 (491)	21.7 (154)	69.2 (483)	19.3 (107)	64.7 (359)	20.6 (97)	55.7 (229)	32.9 (148)	48.2 (202)
Intermediate risk	61.9 (407)	7.7 (48)	46.5 (330)	4.7 (33)	38.6 (214)	2.9 (16)	30.6 (144)	2.4 (10)	7.1 (32)	0 (0)
Low risk	8.5 (56)	0 (0)	3.2 (23)	0 (0)	1.1 (6)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)
Total sum of high risk group, according to priority list and SCORE chart	22.5 (148/657)	85.9 (536/624)	39.5 (280/709)	88.7 (619/698)	48.6 (269/554)	91.4 (507/555)	57.3 (270/471)	89.5 (368/411)	84.0 (378/450)	91.6 (384/419)

*One or more of following criteria present: myocardial infarction, stroke, antihypertensive treatment, diabetes, cholesterol ≥8 mmol/l, systolic blood pressure ≥180 mm Hg, diastolic blood pressure ≥110 mm Hg.
†Extrapolation to 60 years for ages 40, 50, and 55 (denominator is number of individuals in each cohort).
‡Mostly explained by missing data on smoking habits.

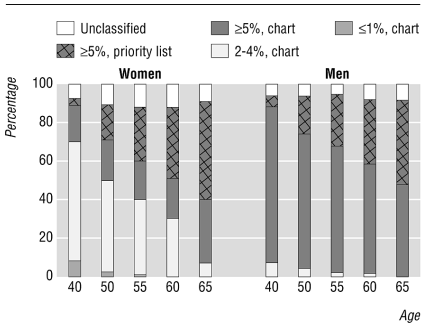

Fig 1 Distribution of risk categories for cardiovascular disease when risk is extrapolated to 60 years, as recommended by the 2003 European guidelines

50 as at high risk for fatal disease. No men aged 40 or older would be classified as at low risk.

Strengths and limitations of the study

The population of the Nord-Trøndelag health study 1995-7 (HUNT 2) is well defined, considered fairly representative of Norway, a country which contributed substantial amounts of data to the systematic coronary risk evaluation project.[5] Compared with other European high risk regions included in the systematic coronary risk evaluation project or the monitoring trends and determinants in cardiovascular disease (MONICA) project (third phase, 1992-4),[10] the population did not differ significantly for cholesterol levels and smoking habits. Blood pressure levels were higher in the Nord-Trøndelag population than in most comparable countries, but lower than in Finland.

The adjustments we made to adapt the data from the Nord-Trøndelag health study to the priority list of the European guidelines, should not significantly affect our main results. People with self reported angina, peripheral artery disease, and high levels of low density lipoprotein cholesterol were not automatically assigned to the high risk group. This contributes to a conservative estimate of the group before evaluation using the chart. Patients with diabetes type 1 without microalbuminuria, however, were included, as were patients receiving treatment for hypertension, irrespective of blood pressure levels. However, all patients with diabetes type 1 and people receiving antihypertensive treatment require a level of attention similar to that of people recently diagnosed as at high risk. We have no specific information on the use of lipid lowering drugs among the participants of the Nord-Trøndelag health study. To the extent that our population may have included patients receiving such treatment, this would contribute to a conservative estimate of the high risk population.

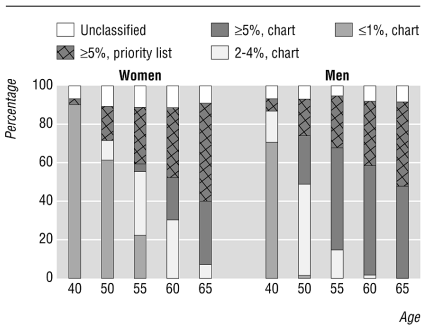

Fig 2 Distribution of risk categories for cardiovascular disease with reference to person's age (not extrapolated)

Applicability of 2003 European guidelines

Our findings can be discussed with regard to three explicit objectives of the guidelines—that is, the development of a risk estimation system intended for adaptation at national or even local level; a tool for prioritising patients; and an aid to individual risk communication and counselling.

Adaptation at national level

A paramount aim of the systematic coronary risk evaluation project was to encourage development of national guidelines on prevention of cardiovascular disease.[5 6] Applying the Framingham risk equation to European countries overestimated the risk of cardiovascular disease.[4 5] This highlights the importance of evaluating risk scoring systems against epidemiological data from the population to be screened before implementation in clinical practice.[13] In addition, a country can show regional differences in morbidity and mortality.[4] A dichotomisation of Europe into high risk and low risk regions may maintain the earlier introduced imprecision of the risk assessment. Whether the high risk chart applies to Norway has yet to be investigated.

Tool for prioritising patients

The 2003 European guidelines seem to be intended as a tool to define the priorities to be set, given limited resources. We found that the guidelines are unlikely to serve as an effective tool for prioritising Norwegians, as they classify an unreasonable number of people as at high risk. Extrapolation of risk to 60 years contributes strongly to this and implies that no men aged 40 or older and only a few women can be considered as at low risk for cardiovascular disease. Absence of extrapolation, however, makes it theoretically impossible for someone aged 40 to be classified as at high risk on the basis of the systematic coronary risk evaluation chart. So whereas extrapolation of risk leads to an overwhelmingly large high risk group, lack of extrapolation may lead to down prioritising of younger people who might benefit from early intervention.

Tool for counselling in clinical practice

The vision of the Third Joint Task Force was to make the guidelines (or adapted ones) part of standard daily clinical practice throughout Europe.[6] The European Society of Cardiology encourages visitors to its website (www.escardio.org) to include these guidelines in their handheld digital systems. The guidelines are therefore clearly recommended for direct use in counselling in clinical practice. Several ethical dilemmas may be linked to implementation of the guidelines in clinical practice. These arise from the likelihood of overestimating someone's true risk for cardiovascular disease. People who contributed data to the systematic coronary risk evaluation project were mostly recruited in the 1970s and 80s (Norway, 1974-8). Since the beginning of the 1970s, mortality from cardiovascular disease has decreased by 30%-50% in western Europe.[1] Lifestyle and body composition in the Norwegian population has also undergone important changes.[14] A given combination of the relevant risk factors for cardiovascular disease is likely to predict a lower mortality risk today than 25 years ago. The systematic coronary risk evaluation project[5] does not discuss the problem of retrospective risk bias.[4 13] A Norwegian group on cardiovascular disease has

What is already known on this topic

Clinicians are urged to implement clinical guidelines in everyday practice

Clinicians show limited adherence to medical guidelines that target asymptomatic conditions

What this study adds

Implementation of European guidelines to prevent cardiovascular disease would label most people in an unselected Norwegian population at high risk of fatal disease from age 40

The validity of the evidence base of the guidelines is questionable and predicts practical and ethical dilemmas related to resource allocation and clinical counselling

The size of the population at risk should be estimated before clinical guidelines are issued

suggested that a 5% risk for mortality in 1985 may correspond to a 2.5% risk in 2003.[15] We question whether it was scientifically justifiable to include the risk charts of the systematic coronary risk evaluation project[5] in guidelines intended for implementation in a clinical setting[6] before validation in a contemporary context.

Any overestimation of a person's risk for cardiovascular disease can have important implications. Apart from causing unnecessary concern, it undermines the patient's informed choice for intervention. It is also likely to increase prescribing costs and affect life insurance premiums.[4 16] As yet little scientific knowledge is available on how the communication of this kind of risk affects people's understanding of themselves, their bodies, and their lives.[11 17 18]

Process for development of guidelines

When guidelines class most adults in one of the world's longest living and healthiest populations[19] as at high risk and therefore in need of maximal clinical attention and follow-up, it raises several scientific and ethical questions.[20] The finding predicts major dilemmas related to workload and resource allocation,[21] even in Norway where the political, economic, social, and medical circumstances[6] reflect excellent access to health care by international comparison,[19] and the per capita expenditure on health is among the highest in the world.[19] It may be time to reconsider the aims and means of prevention of cardiovascular disease and the process of developing guidelines.[22]

Methods for the development of guidelines for prevention of disease should be scientifically consistent so as to ensure that concordance with guidelines is practically feasible and likely to result in the desired outcomes.[23] Evidence from biomedical research has limited meaning in isolation; it must be regarded in light of the overall vision, values, strategies, and resources that exist in the area of preventive medicine, both nationally and internationally.[22–24] Despite the contribution of numerous experts and professional societies, it seems that authoritative clinical guidelines on the basis of the systematic coronary risk evaluation project may be an example of premature application of medical technology in routine clinical practice.

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Competing interests: None declared.

Ethical approval: Surveys in the Nord-Tröndelag health study were approved by the Norwegian data inspectorate and the regional committee for ethics in medical research.

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APPENDICES

12. APPENDICES

12.1 APPENDIX. English translation of relevant HUNT 2 survey questions

On this page is an English translation (text from HUNT website) of the particular HUNT 2 survey questions which are used in Papers IV and V. The original Norwegian version of the questionnaires is available at http://www.hunt.ntnu.no.

FROM QUESTIONNAIRE 1: CARDIOVASCULAR DISEASES, DIABETES

Have you had, or do you have			
A myocardial infarction	Yes	no	Age first time
Angina pectoris (heart cramp)			Years
A stroke/brain haemorrhage			Years
Diabetes (sugar disease)			Years
Are you taking medication for high blood pressure?			
Just one cross			
Now ☐			
Did previously, but not now ☐			
Have never taken it ☐			

SMOKING

Do you smoke yourself? YES NO

Cigarettes daily?		
Cigars/cigarillos daily		
Pipe daily?		

Have never smoked daily…… *Put a cross* ☐

FROM QUESTIONNAIRE 2: ILLNESS IN THE FAMILY

Put a cross for the relatives who have or have had any of the illnesses. Put a cross in „none" if none of these relatives has had these diseases: *Possibly several crosses on each line.*						
	Mother	Father	Brother	Sister	Child	None
Stroke or cerebral haemorrhage	☐	☐	☐	☐	☐	☐
Heart attack before age of 60	☐	☐	☐	☐	☐	☐

12.2 APPENDIX. From Antiquity to the foundations of EBM: some historical notes and personal reflections on the premises for contemporary medical consultations

In the introduction to his book *Doctoring*, Eric J. Cassell notes that (1997:10):

> The fundamental knowledge base for primary care remains the traditional preclinical science of medicine. It is the foundation from which modern Western medicine derives its legitimacy. It is the basic source of knowledge about nature as it is expressed in the body in health and disease. It is about (...) body-as-nature.

In order to appreciate that, which goes on in consultations between patients and doctors in every-day Western medicine, some basic reading of the history of Western medicine has proved helpful to me. In this informal essay, I will outline some historical milestones that lead up to medical knowledge and reasoning, as we know it today. In addition, I will add some personal reflections. The final destination of this historical journey is a previously quoted (see chapter 2.2.4) description of *the biomedical way of thinking* about disease and suffering, as formulated by professor of family medicine Ian McWhinney in 1989. My main historical guide has been professor of the social history of medicine Roy Porter's (1926-2002) book *The greatest benefit to mankind. A medical history of humanity* (1998).[152] To look further into various details, I have also consulted web-based encyclopaedias, in particular the open-access Wikipedia (www.wikipedia.org).[153] As I find US historian of science Thomas Kuhn's notion of scientific *paradigm shifts* useful to help conceptualise the development of medical theory and practice, I will begin this essay with a brief introduction to Thomas Kuhn's (1922-1996) works.

The structure of scientific revolutions

This is the title of Kuhn's most renowned work from 1962 (Kuhn 1970). It contains an analysis of the history of science and popularised the terms 'scientific paradigm' and 'paradigm shifts.' The roots of the book date back to 1947, when Kuhn was asked to teach a science class for humanities undergraduates at Harvard University, with a focus on historical case studies. Kuhn later said that, until then, "I'd never read an old document in science." What he discovered as he now did this, was how astonishingly unlike Aristotle's Physics was from Isaac Newton's works. Kuhn came to the conclusion that Aristotle's way of thinking should not be considered as primitive or "bad Newton" but, rather, as fundamentally *different* from Newton's. With the general acceptance of Newton's mechanistic world-view, alternate ways of thinking and knowing about the world, such as those formulated by the ancient Greeks, had been lost.

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[152] Roy Porter is also author of traditional historical works such as The Cambridge Illustrated History of Medicine, Cambridge University Press, 1996.

[153] Wikipedia is a multilingual, web-based, free-content encyclopaedia written collaboratively by volunteers. The project began in 2001 and is operated by the non-profit Wikimedia Foundation. Articles in Wikipedia are regularly cited by the mass media and academia. Editors are encouraged to uphold a policy of "neutral point of view" under which notable perspectives are summarized without an attempt to determine an objective truth. Yet due to its open nature, the status of Wikipedia as an exact reference work has evidently been somewhat controversial.

The aim of science is *to find a model that will account for as much of one's observations as possible in a coherent framework*. But in every community of scientists, there are according to Kuhn individuals who are bolder than the rest and occupy themselves with observations that do not fit with the current dogmas and challenge long held, taken-for granted assumptions. If in time, solidification and unification of a challenging scientific view is achieved, it will replace the old. A *paradigm shift* has then occurred. Some examples of Kuhn-ian paradigm shifts are: the transition from a Ptolemaic cosmology to a Copernican one (from 1543, and later promoted by Kepler and Galileo), the unification of classical physics by Newton into a coherent mechanical worldview, the transition between the worldview of Newtonian physics and the Einsteinian relativistic worldview, and the development of Darwin's theory of evolution by natural selection, which overturned theories of evolution by inheritance of acquired characteristics.

The most common criticism of Kuhn, from historians of science, is that the notion of a clean paradigm shift only seems to apply when one takes a very abstract view of the history of any given theory transition. When looking at the details, it becomes increasingly difficult to discern coherent 'paradigms' to shift in to or out of. However, paradigms do become quite apparent if one examines pedagogical practices such as textbooks, and this was largely how Kuhn developed his theory. Once a paradigm shift has taken place, textbooks are rewritten, and according to Kuhn, they tend to outline the history of science as a process of increasing sophistication which inevitably builds up to the currently established understanding of the world. The texts thereby convey a tacit belief that in due course, all phenomena will be accounted for in terms of the new established framework. Kuhn believes that what scientists spend mostof, if not all of, their careers doing, is participating in a process of puzzle solving within a given frame. The previous successes of the established paradigm instill great confidence that a solution to the puzzle exists, although very hard to find. Kuhn calls this process of optimistic puzzling *Normal science*.

As a paradigm is explored to the limits of its scope, however, *anomalies* – i.e. failures of the current paradigm to take into account observed phenomena - accumulate. Their significance is judged by the practitioners of the discipline. Some anomalies may be dismissed as errors in observation. Many anomalies 'dissolve' spontaneously within the established paradigm, with increased scientific refinement and deepening insight. The majority of the scientific community will generally oppose any change of mind, and, according to Kuhn, this is as it should be. In order to fulfil its potential, a scientific community must consist of both people who are bold and people who are conservative. But then, if for instance a gifted scientist recognizes the potential of the new or competing paradigm, greater change will occur. Louis Pasteur (1822-1895) is an example of a brilliant scientist who opened the door to a new scientific paradigm. Pasteur was not the one to propose the germ theory; but he was the one to demonstrate its correctness and convince Europe that it was true. He famously said about scientific progress that "Chance favours the prepared mind".

Opinion is divided on whether or not Kuhn's theory applies to medicine (McWhinney 1989). Kuhn himself maintained that paradigm change occurs in applied disciplines

and even in sub-disciplines. And Ian McWhinney holds the view that Kuhn's theory fits well with the developments in medicine.

Milestone I: Scientific observation in the context of healing-by-relation in ancient Greece

Western medicine is rooted in Antiquity, and the time when Greek medicine became separated from religion around 400 years B.C. Theories of illness and healing thereby became *independent of the supernatural and started to build upon natural philosophy*. Greek medicine emphasised the microcosm/macrocosm relationship, the correlations between the healthy human body and the harmonies of nature. But the new and 'scientific' idea which now emerged was that *man was governed by the same natural laws as the cosmos*. Hippocrates of Cos (460-377 BC) is widely regarded as the most outstanding medical doctor of all times. Roy Porter refers to his "Olympian status in medicine as the champion of bedside experience." Hippocrates appealed to *reason and observation*, rather than to rules or supernatural forces. Ideas of *disease as a syndrome*, a constellation of related signs and symptoms, began to emerge in the Hippocratic school of medicine. Hippocrates however first and foremost worked in an individually oriented cosmology where causes of disease were sought in the realm of the individual patient (Blaxter 2004). Hippocratic doctors presented themselves as "friends of the sick" and focused more on the individual person's subjective *experience of dis-ease* than on *diseases as phenomena* with their own independent existence (ontological entities). In the Hippocratic medical paradigm, disease could not be regarded as separate from the suffering person, and the person could not be regarded as separate from his or her environment. The cornerstone of healing interventions was *diatetica*, and in this era a "dietary regimen" prescribed by a doctor would involve the person's entire lifestyle. Therapy aimed at treating each patient individually and symptomatically, *giving the healing powers of nature a helping hand*. Frequent visits to the patient were recommended, as was an expectant clinical attitude. Clinical acuity and prognostic skills were highly prized. The Hippocratic Oath honoured trust-based and confidential clinical relations. It discouraged heroic interventions. A basic rule of Hippocratic medicine was to avoid doing harm. The Hippocratic Oath foreshadows the paradigm of profession as a morally self-regulating discipline among those sharing craft knowledge and committed to serving others.

The medical heritage of Antiquity, with its emphasis on *lifestyle and harmony*, remained powerful for many centuries. According to Roy Porter, it was authoritative in Western bedside practice until the 18th Century when it was gradually to become challenged by medical practice grounded on *experimental* investigation.

The Greek physician Galen (131-201 AD) who later lived in Rome and served as a court physician to emperor Marcus Aurelius (and made many discoveries of anatomy by way of vivisection of animals), transmitted the heritage of Hippocratic medicine all the way to the European renaissance, which reached its peak in the 15th Century.

The main impact of Hippocratic medicine can be summed up as follows: It taught that understanding of sickness required understanding of nature. And it carved out a distinct role for the unselfish and morally responsible physician.

Reflection 1. How can we conceptualise 'the art of medicine' today?
Before moving more than 1700 years ahead in time, l will mention a paper by Norwegian philosopher Åge Wifstad (Wifstad 2003) who presents German philosopher Hans-Georg Gadamer's (1900-2002) reflections on contemporary and ancient medicine (see also Arnason 2000). In his book *The Enigma of Health*, Gadamer investigates the ancient roots of modern medicine and comes to the conclusion that this medicine "itself represents a peculiar kind of practical science for which modern thought no longer possesses an adequate concept." Our dilemma is thereby, that *in order to accommodate the original meaning of the concept "the art of medicine," we would have to revert to a way of thinking about nature, which is unfamiliar to us.* One may take Aristotle's theory of causality as an illustration. Aristotle recognized four kinds of causes – of which the most important was the "final cause." The final cause was *the aim or goal of something*. Thus, a final cause of rain could be to let plants grow. In the ancient Greek world, the art of medicine was the art of restoring natural equilibrium. In this creative process, the doctor's actions would orchestrate the healing forces of nature – resulting in his own becoming superfluous. And thus healing would occur in such a fashion that the doctor's art could never be proven – not to himself, or to others. Our contemporary notion of *technology* however implies that the ability to produce certain effects in nature can be isolated, objectified, and seen as existing independently of context. This 'new' way of thinking dates back to the scientists of the Scientific Revolution, such as Galileo Galilei.

Milestone II: The Scientific Revolution and the conceptualisation of "nature-as-clockwork"

In Europe around the year 1600, a rapid and fundamental change took place in the theoretical outlook regarding nature. This 'scientific revolution' can – in a simplified fashion, be summarised in connection with four distinctive names:

Galileo Galilei (1564-1642) is seen as the father of 'experimentalism.' He legitimised *observation*, as opposed to pure thinking, as *the* route to authentic knowledge. Galileo's falling body experiments are prime examples of this. Before his time, the Aristotelian belief prevailed that nature should be looked at as it worked on its own. Performing experiments would put nature in 'unnatural' circumstances, and hence the results of an experiment would not agree with the true way nature worked.

Sir Francis Bacon (1561-1626) was an English lawyer, statesman, writer, historian and philosopher who projected (what we would now think of as) the mechanical, experimental philosophy, onto the entire natural universe. Bacon suggested a system of "true and perfect induction," which he proposed as the essential foundation of scientific method and a necessary tool for the proper interpretation of nature. It can be argued

that the modern idea of technological "progress" (in the sense of a steady, cumulative, historical advance in applied scientific knowledge) began with Bacon, who maintained that *knowledge is power*. Bacon's investigative method was put forward in his work *Novum Organum* (the New Organ) in 1620, and was supposed to replace the methods put forward in Aristotle's *Organum*.

Robert Boyle (1627-1691) set about regularising Galileo's experimental work as characterised by his reports of "falling bodies experiments" in a broad manner. Although Boyle's research and personal philosophy had its roots in the alchemical tradition, he is widely regarded as the first modern chemist. He also made various great accomplishments in physics (i.e. Boyle's law). Boyle's book *The Sceptical Chemist* (1661) outlines chemistry as the science of the *composition of substances*, not merely an adjunct to the arts of the alchemist or the physician. He advanced towards the modern view of elements as the indecomposable constituents of material bodies. He further supposed that the elements were ultimately composed of particles of various sorts and sizes. He was also interested in the chemistry of combustion and respiration, and made experiments in physiology. He was however hampered by the "tenderness of his nature" which kept him from doing anatomical dissections, especially of living animals, which he otherwise thought to be most instructive.

Sir Isaac Newton (1642-1727), the English physicist, mathematician, astronomer and philosopher, has by many been regarded as the most influential scientist ever. In 1687, he published the *Philosophiae Naturalis Principia Mathematica*, where he described universal gravitation and, via his laws of motion, laid the groundwork for classical mechanics. A simple illustration of how Newtonian discoveries could affect people's perception of nature is that he was the one to discover that the spectrum of colours observed when white light passed through a prism is inherent in the white light – and not added by the prism.

The main impact of the Scientific Revolution is that from now on, experimental natural philosophy was thought to offer the most persuasive scientific model.

For a long period to follow, bedside medical *practice* was quite unaffected by the Scientific Revolution. Therapeutic interventions remained grounded in tradition. Major milestones were however passed in the area of anatomy and physiology. Andreas Vesalius had published his anatomical atlas *De humani corporis fabrica* (On the Workings of the Human Body) already in 1543; this was the first major anatomy work since the time of Galen. William Harvey published his work *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (An Anatomical Exercise on the Motion of the Heart and Blood in Animals) in 1628, where, based on scientific methodology, he argued for the idea that blood was pumped around the body by the heart – before returning to the heart and being re-circulated in a closed system. This overturned the accepted ancient model which identified venous (dark red) and arterial (brighter and thinner) blood, each with distinct and separate functions.

In the late 17th and early 18th Centuries, medical knowledge was gathered ever more in accordance with the new scientific paradigm. Opening up bodies – dead human

cadavers and living animal ones – now became the general prescription for true medical knowledge. The word autopsy (Greek: *autopsia*) literally means "to see with one's own eyes." In the late 1660s, the microscope was taken in use, and this advanced the reductionistic, mechanical model of living beings even further.

The British physician Thomas Sydenham (1624-89), sometimes referred to as "The English Hippocrates," is known for his careful observations of epidemic disease in London. A man with a very scientific mind, he was still sceptical to the idea that learning about disease should mainly be done by way of dissection. Sydenham told a young student that "… my butcher can dissect a joint full and well; young man (…) you must go to the bedside…" Having himself observing the effect of one specific remedy (the cinchona bark which contains quinine) used against the specific disease pattern known as *ague* (from Latin *acuta*, literally, sharp fever, i.e. recurrent malaria),[154] Sydenham's mind was however prepared for the emerging theory that *diseases should be seen as entities that existed independently of the sufferer*. In the words of Sydenham: "all disease should be reduced to definite and certain *Species*… " (Porter 1997:230).

From the perspective of medicine, Roy Porter describes philosopher and mathematician René Descartes (1596-1650) as "the towering thinker of the scientific revolution." As a dedicated spokesman of the emerging mechanical philosophy, Descartes rejected the ancient Greek notion of final causes. *There were from now on no inherent goals, emotion nor intelligence in nature*. Where nature had previously been seen as a living entity, the Scientific Revolution viewed nature as *matter*, which follows natural, physical laws. Whereas Augustine and many other medieval thinkers understood the body as something corpse-like, unless 'infused' with soul, *Descartes argued that vitality simply arises from the body's own mechanical processes* (Leder 1998). Thereby, Descartes compared expressions of life to "a watch or other automaton, when it is wound up and contains in itself the corporal principle of those movements" (Descartes quoted in Leder 1998:119). To Descartes, as to Bacon, *the way of conceptualising the world was intertwined with a project of mastery*. In Cartesian thinking, there is a direct link between "knowing the force and action of fire, water, air, the stars, heavens and all other bodies that environ us" and "employing them in all those uses to which they are adapted, and thus render ourselves masters and possessors of nature" (Descartes in *Discourse on Method*, quoted in Leder 1998:119). The idea that knowledge grants us power over nature was alien to the ancient Greek and medieval thinkers. In a universe where a notion of final causes existed, even natural bodies were perceived to be alive in a sense, and exhibiting their own intrinsic ends. Descartes´ material world – which he called *res extensa* – was however devoid of all intrinsic subjectivity. Nature could thereby be manipulated, shaped and exploited. Drew Leder describes this as "a crucial shift from passive contemplation to the active manipulation which characterises the modern age" (Leder 1998:120). This step in the history of science links up to the teachings of the philosophers Heidegger and Jonas, who were preoccupied with the way modern technology leads us to see nature – and to a certain extent even human beings – in terms of standing-reserve, ready for use (see chapter 2.4.2).

[154] Roy Porter states that arguably, this may have been the first effective, specific drug therapy in Western medical history.

One central claim of Descartes was that the *immaterial mind* and the *material body* causally interact (i.e. mental events cause physical events, and vice versa). Descartes never worked out *how* mind and body interacted, however, but his suggestion was that the site of interaction was the pineal gland. The Cartesian "mind-body dualism" is still a tacit premise for mainstream biomedical research and practice (Bracken 2002). As previously outlined, Drew Leder has written about the fundamental impact of Cartesian thinking in modern medicine in the essay "A tale of two bodies: The Cartesian corpse and the lived body" (Leder 1992, re-published 1998).

Reflection 2: "Time to remove the mind-body split."[155] In the closing chapter of his renowned book *Steps to an ecology of mind*, anthropologist Gregory Bateson wrote: "When you separate mind from the structure in which it is immanent, such as human relationship, the human society, or the ecosystem, you thereby embark, I believe, on fundamental error, which in the end will surely hurt you" (Bateson 1972:493).

Current thinkers (Moerman 2002; Szawarski 2004) believe that human healing processes can be conceptualised as composed of three elements:
1. Self-healing (physiological processes)
2. Specific treatment effects (i.e. aspirin, antibiotics), and
3. Contextual effects, which may relate to the so-called *placebo* effect. This is healing which is elicited specifically by experiences of meaning and context, such as a trusting doctor-patient relationship.

The long-time implications of the Cartesian dualism have been to exclude the third element from the domain of medical interest. Modern medicine thereby turns its back on its most fundamental therapeutical potential. In his latest work (1987), Gregory Bateson writes that *a science about man that does not even understand the placebo phenomenon is on the wrong track*.

The phenomenon of *placebo* can be seen as an artefact of the biomedical paradigm (Ekeland 1997 and 1999). Within a theoretical framework that is not based on the premises of Cartesian dualism between body and mind, there would be no placebo phenomenon to explain. But in the context of contemporary biomedicine, *only material causes are considered as real*. The physiology of the placebo response can thereby be described within the existing paradigm, but the phenomenon cannot be *explained within the biomedical frame of thinking*. In other words, we are dealing with a striking *anomaly*, according to Thomas Kuhn's terminology.

Milestone III: Reason will solve every problem known to man: the age of Enlightenment in Europe

The *Age of Enlightenment* refers to the late 17th and 18th century in European philosophy and a historical intellectual movement, "The Enlightenment". This time period saw a continued rise of empirical philosophical ideas in the tradition of the scientific

[155] This is the title of a BMJ editorial by Bracken and Thomas, 2002.

revolution, and their application to politics, economy, government and sciences such as physics, chemistry, biology and medicine. Newton's conception of *the universe based upon natural and rationally understandable laws* was at the core of Enlightenment ideology. And what is particularly noticeable, is that the Enlightenment movement also advocated *rationality as a means to establish an authoritative system of ethics, aesthetics, and knowledge*. As Descartes had said, "the key to the universe is its logical rather than spiritual order" (Descartes quoted in Gordon 1988:24). The intellectual leaders of this movement regarded themselves as courageous and elite and saw their purpose as leading the world toward progress and out of a long period of doubtful tradition, full of irrationality, superstition, and tyranny. This Enlightenment movement came to provide the cultural basis for the American and French Revolutions.

In accordance with nature as a whole, medical researchers now began to conceptualise disease as something orderly and predictable. And medical reasoning disconnected itself completely from religion. Disease was now regarded as the result of natural mechanism, not of sin or divine punishment, as had been thought for centuries (Gordon 1988). In the 18th century, scientific medicine was however far from a uniform endeavour. It was characterised by a number of rivalling schools and thoughts. Some schools gave more room for so-called *vital life-forces* than others, who conceptualised human health and disease in a purely mechanistic fashion.[156] There was agreement, however, that medicine was remote from gaining the perfection attained in areas such as experimental physics and chemistry.

Although many of the ambitious clinicians of the time acknowledged that Thomas Sydenham was right when he said that a good clinician had to know his diseases as well as his patients, most of them still made their name as men of letters, philanthropists or improvers. But times where now to change, according to Enlightenment philosophers. As Bacon had claimed, *science and technology would ultimately come to enhance man's control over nature, and social progress, prosperity and conquest of diseases would follow*. French Enlightenment philosopher, mathematician and political scientist Marquis de Condorcet (1743-94) made the following visionary statement regarding medicine, typical for this epoch:

> Improvement of medical practice, which will become more efficacious with the progress of reason and of the social order, will mean the end of infectious and hereditary diseases and illnesses brought by climate, food and working conditions. It is reasonable to hope that all other diseases may likewise disappear as their distant causes are discovered (Porter 1997:245).

We now pass the milestone where Swedish botanician Karl von Linné created new taxonomies for natural history (1735). And in this tradition, ambitious attempts to classify diseases would follow. One of these was Cullen's classification system (1785), which defined the three general disease categories *the pyrexias, the neuroses*, and *the cachexias*. His fourth category encompassed *local disease* (Source: Encyclopaedia Britannica 1911 version). In the footsteps of Cullen followed men such as Benjamin

[156] Following in the foosteps of Newton, Duch professor Boerhaave (1668-1738) lead the application of physics to medicine. Boerhaave perceived that health and sickness could be seen as expressions of forces, weights and hydrostatic pressures and saw health as some sort of hydrostatic equilibrium (Porter 1997:246).

Rush, a founding father of American medicine and a signatory of the US Declaration of Independence. Rush added a disease category called *hypertension*. He was among the most eager promoters of copious bloodletting, a therapeutical intervention, which inflicted much harm[157] until it was finally abandoned, thanks to sceptical and independent, academic minds such as the French physician Pierre Louis (see below).

According to Roy Porter, hardly any 18th century scientific advance helped heal the sick directly. And in addition to adverse effects of direct heroic therapeutic actions such as blood-letting, the new lying-in hospitals featured dramatic mortality rates for reasons that were little understood, – until Hungarian-Austrian Ignaz Semmelweiss (1818-1865) figured out that many cases of fatal disease could be prevented by the simple and unsophisticated measure of hand washing.[158]

"Morti Vivos Docent"[159]

In the late 1700s, a new type of disease classification emerged, based on morbid anatomy. *Morbid anatomy in the dead would from now on be regarded as the main clue to understanding sickness in the living*. Italian Morgagny published his radically new classification system in 1761, called *De sedibus and causis morborum* (On the Sites and Causes of Disease). It was based on visual accounts of 700 autopsies. Morgagny did not include any speculation about causes. His work received instant recognition, and researchers in other countries rapidly followed suit. Patho-anatomical descriptions started to appear in textbooks, describing phenomena such as emphysema, liver cirrhosis and ovarian cysts. Around 1800, Paris clinician-pathologist Xavier Bichat (1771-1802) published a seminal work on anatomy, introducing the doctrine of tissues (connective, muscle, nerve, etc.). His works laid the foundations for 19th century patho-anatomy. In 1801, Bichat advised young doctors that "You may take notes for 20 years from morning to night at the bedside of the sick, and all will be to you only a confusion of symptoms... a train of incoherent phenomena." Start dissecting bodies, he stated, "and this obscurity will soon disappear." With Michel Foucault's work *The Birth of the Clinic: An Archaeology of Medical Perception* in mind, Roy Porter notes that "here is the medicine of the all-powerful gaze." And as Foucault also noted, in this era of French hospital medicine, 'the natural death' gradually becomes replaced by 'the pathological death.' Death is no longer perceived as something coming from outside life; it was contained within the body, where physiological and pathological process battled for supremacy (see Armstrong 1995).

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[157] On the morning of December 14th 1799, former American president George Washington (otherwise in a state of reasonably good health) woke up with an aggressive throat infection, presumably an epiglotitis (in today's terminology). During the day to come, which ended with his death at 10.20 p.m., Washington was bled four times; the total amount of blood withdrawn has been estimated to 2,4 litres (Morens DM. *Death of a president*. N Engl J Med 1999;341:1845-50).

[158] The story of Semmelweiss is perhaps the most illustrative example of how authority-based medicine can hinder professional progress. Norwegian author Jens Björneboe contemplates this issue in his play Semmelweiss (1969).

[159] Latin: "The dead teach the living."

Milestone IV: The birth of the Clinic

The French revolution and its aftermaths had enormous implications for the development of Western medicine as a whole. David Armstrong has described how medicine moved from a two-dimensional to a three-dimensional framework at this point in time. In traditional *bedside medicine* until now, the headache or the abdominal pain, as it presented itself in the clinical encounter, 'was' the patient's illness. What happens now, in French hospital medicine, is that the simple relationship between symptom and illness/disease will become reconfigured into a three-dimensional framework consisting of the *patient's symptoms,* the *signs observed by the doctor,* and *the 'objective' pathology*, originally to be established by post mortem examination (Armstrong 1995).

After the French revolution, the authorities of the *ancien régime* were rejected, and the revolutionary young doctors were men who prized hands-on experience. A distinctive and influential *school of Paris hospital medicine* developed; based on careful, scientific observation of patients. Thereby, the individually oriented approach to patients where causes of disease were to a high degree sought in the context of personal attributes, was once and for all abandoned. In *Doctoring* (1997:48), Eric J. Cassell underlines that "It is difficult to overestimate the brilliance of the Paris physicians of the 1830s, the discoverers of scientific medicine."

French hospitals had traditionally been religious foundations devoted to tending to the sick. In the post-revolution period, patients were to a lesser extent fee-paying, and thereby, control to an increasing extent passed from the patient to the doctor. In this epoch, the elite physicians turned the hospitals into what Roy Porter describes as "scientific machines for investigation of diseases and teaching." Interest turned to pathology, rather than the patient (Blaxter 2004). Poor people had ready access to the hospitals, but in many respects they were commodified as "clinical material." Nuances between different, individual patients were not the focus of attention; "the discoverers swept away layers of confusing social, psychological, and personal issues as irrelevant for scientific medicine" (Cassell 1997:48). *The doctor's task was from now on seen as that of establishing the patterns of pathology*. 'The new doctors' were clinician-pathologists who meticulously documented their findings using the investigative tool of clinical-pathological correlation. And they were highly successful in doing so. French physician René-Théophile-Hyacinthe Laënnec (1781-1826) was for instance able to describe one disease, tuberculosis, in all its facets, without knowing anything about its causing agent (Cassell 1997:48). A German physician named Robert Volz (1806-82) is however said to have expressed concern over the overall development in Paris hospital medicine in this epoch. He noted that "The sick person has become a *thing*" (Porter 1997:311).

The 'objective' physical examination

In early 19th Century elite Paris medicine, physical examination of living patients gradually attracted more attention. Laënnec invented the stethoscope in 1816, and this event can be seen as opening the door to *a new medicine of objective physical signs*. As one

19th Century physician expressed it: "We anatomise by auscultation – if I may say so – while the patient is yet alive" (quoted in Leder 1998:120). The stethoscope became a symbol of scientific medicine, as it paved the way for the 'dissection' of the living body, analysing it into its component parts, exposing what is otherwise concealed. This development obviously had profound implications for the doctor-patient relationship in the future. *By bypassing the patient's unreliable account of symptoms, diagnosis could now be rendered more reliable through objective signs* (Porter 1997:309). Many foreign students received their medical education in Paris in this epoch. Following the French example, medical education in many countries now grew more systematic and scientific, with a main focus on drilling students in the discipline of *diagnosis*.

The shift from reliance upon subjective symptoms – reported by sufferers – to objective signifiers of disease – reported by clinicians – pointed in direction of yet another new branch of medical science; that of *pathophysiology*. And by the 1850s, the discipline of modern laboratory medicine began to emerge. In this epoch, Rudolf Virchow (1821-1902) also did his pioneering work in *cellular pathology*.

Experiments with drugs and introduction of the numerical method to test treatments

From around 1810, organised experimentation into the action of drugs started. In France, François Magendie (1783-1855), a founding father of both experimental physiology and experimental pharmacology, carried out groundbreaking experiments on the effect of Javanese arrow poison (the active component was later shown to be strychnine), morphine, emetics (ipecacuanha), quinine, caffeine, atropine, and several other drugs. He also made important discoveries related to the nature of the nerve system. Magendie was concerned with the topic of *vitalism*, the branch of medicine that assumed existence of a vital force in living organisms. The force of life, as he saw it, would however have to be explained through experiments on living animals. Magendie saw the aims of science as that of replacing *phenomena* with *facts* and *impressions* with *evidence* (Margotta 1996).

In parallel with Magendie's research, another methodological invention was made that came to influence the development of modern medicine strongly. Inspired by the quantifying spirit of the Enlightenment, physician Pierre Louis (1787-1872) conceived the idea of *testing therapies using numerical methods*, thus introducing statistics to medicine and paving the way for the clinical trial. His ideas were first tested out on the therapeutic tradition of blood-letting (phlebotomy). The medical authorities of that time did not allow him to leave any patient untreated, so Louis had to compare blood-letting at various stages of disease. His conclusion was that it did not make people better. Apparently, Louis came to the general conclusion that medical interventions of the time rarely cured patients, and he came to distrust the extravagant success claims made by some of his contemporary colleagues.

Reflection 4. The "philosophical origins" of Evidence-based medicine. At this point in history, the methodological repertoire has in fact been laid out for what came to be known as Evidence Based Medicine (EBM) more than a century later. In the introduc-

tion to the main teaching book on EBM (1997), David Sackett and co-workers write that the scientific contributions of French physicians Bichat, Magendie and Louis have been among their greatest sources of inspiration. The founders of EBM state that its philosophical roots can be found in French hospital medicine. If they truly mean that EBM has a philosophical basis, however, this would be a philosophy of human disease, suffering and healing based upon the following elements (Ekeli 2000):

- death, the medical gaze, the site, as defined by the autopsy-tradition of Bichat,
- biomedical facts and evidence, – as defined by Magendie's experimental approach,
- control groups and statistics, – as introduced by Louis.

Diagnostic technology included in the institutional bedside routine

Except for the stethoscope, the clinical medical examination was not much affected by technology until the late 1800s. But in 1886, the stethoscope was accompanied by the sphygmomanometer developed by Riva-Rocci (see Appendix 4). And thermometry – the science of temperature patterns in various diseases – was formally developed in large observational studies in the 1860s. *The observational tradition of pathology was thereby being systematically translated into recordings made by instruments*, reinforcing the notion that specific, objective and preferably graphic data were fundamental to clinical practice. Roy Porter notes that (1997:346): "By 1900 it was becoming possible to understand the patient not by his story, nor even simply through pathological signs ascertained by the 'medical gaze', but by ceaseless physiological monitoring." Among practicing clinicians, however, there appears to have been some controversy surrounding this development, as some believed it to represent a form of clinical de-skilling. But in the context of the large hospitals, measuring devices that lent themselves to routines (that could in part be delegated to assistant personnel) were now incorporated. By 1912, the Massachusetts General Hospital required blood pressure measurements at all admissions (Porter 1997:344). Routine use of laboratory tests was also on its way to clinical practice. The renowned Sir William Osler (1849-1919) whose humanistic and humble spirit is still honoured, described the hospital ward laboratory "as essential to the proper equipment of the hospitals as the interns. They are to the physician just as the knife and scalpel are to the surgeon" (Porter 1997:347).

Medicine divided about its future

According to Porter, medicine was becoming "deeply divided about its future" in the late 19th Century. One of the important general ideas of the 19th Century was *division of labour*. In clinical practice up to this time, specialised medical procedures such as phlebotomy and surgery had been left to workers with a lower rank. The ideal clinician had been the generalist, in accordance with the Hippocratic notion that disease was best regarded as a constitutional phenomenon, not a local matter. But now, *the general idea of medical specialisation achieved increasing adherence*. Hospital medicine was to an increasing extent to become organised according to affected body parts and local sites of disease. Specialisation however did encounter scepticism. In 1900, for instance, the journal *The General Practitioner* stated about medical specialists that

> their minds are narrowed, judgement biased and unbalanced by disproportionate knowledge of one subject.

It was also stated that the patient would suffer because the specialist "knows nothing of the constitutional idiosyncrasies of the individual, which are essential to diagnosis and treatment" (Porter 1997:388).

Outside the hospitals, the Hippocratian relationship between physician and patient, based on care, courtesy and compassion still stayed alive and relatively well. Private medical practice was however market-driven and based on fee-for service. An increasing gap was now developing between the idea of medical practice as something *independent and personalised*, and the idea of organised and coordinated *state medicine and public health regulation*, where doctors would be seen as saviours of humanity or as 'medical police,' depending on the context.

Interestingly enough, the emergence of increasing medical specialisation was paralleled by the emergence of various, new holistic healing movements who rejected the ethos of orthodox reductionist medicine.[160] Porter reflects on this time period: "Alternative medicine's preoccupations highlight the ambiguities in nineteenth-century medicine. Its new scientific and professional movement generated counter-trends (…) While people wanted their diseases to be cured, they were also seeking far more from medicine: explanations of their troubles, a sense of wholeness, a key to the meaning of life" (Porter 1997:396).

Reflection 4: At this point, medical knowledge is soon ready to unchain its therapeutical powers. There is now only one major chapter missing before the Cartesian mechanist medical knowledge base became comprehensive enough to lay out the premises for the *therapeutic revolution*, an epoch which started in the late 1930s and lasted into the 1980s, as outlined in James le Fanu's book *The rise and fall of modern medicine* (1999). The missing chapter began as French chemist and microbiologist Louis Pasteur confirmed the *germ theory of infection* in 1878. In a short time, isolation of different bacteria and development of various vaccines followed. The scientific area of *bacteriology* immediately came to strengthen the notion that specific causal agents lead to specific disease entities. The rational strategy to prevention and treatment of disease would thereby be to look for *specific biomedical interventions that would remove or destroy the causal agent*.[161]

So where do we go from here?
As a discipline, medicine needs to stand on two feet; one biomedical leg and one humanistic leg (Hetlevik 2004), see figure 12.2. In the four centuries since Descartes, the scientific medical community has however been exercising the biomedical leg to an ever increasing extent, at the expense of the humanistic leg. Medicine is thereby – as I see it, and as has been outlined in all papers of this thesis – about to lose its theoretical balance as a scientific approach to human disease, suffering and healing (see figure 12.2).

[160] A variety of healing movements were established throughout the 1800s. The founder of homeopathy, Hahneman, first formulated his methodological principles in Handbook of rational healing in Leipzig in 1810. Hydrotherapy (water cure) became increasingly popular throughout Europe in the mid 1800s. Chiropractics were established in 1895, etc.

[161] Examples of cures (or prevention) for specific causal agents: Pasteur began developing vaccines in 1879. The bacteriostatic sulfa drugs were developed in the 1930s. Penicillin was introduced in the clinical setting in 1941.

In 1989, and with reference to Thomas Kuhn's model, Ian McWhinney described the contemporary biomedical model in terms of *the Old paradigm* (as referred in chapter 2.2.4). It is in fact quite striking how little the medical model has changed since the times of Louis Pasteur:

> Patients suffer from diseases which can be categorised in the same way as other natural phenomena. A disease can be viewed independently from the person who is suffering from it and from his or her social context. Mental and physical diseases can be considered separately, with provision for a group of psychosomatic diseases in which mind appears to act on the body. Each disease has a specific causal agent and it is a major objective of research to discover them. Given a certain level of host resistance, the occurrence of disease can be explained as a result of exposure to a pathogenic agent. The physician's main task is to diagnose the patient's disease and to prescribe a specific remedy aimed at resolving the cause or relieving the symptoms. (...) The physician is usually a detached observer and the patient a passive recipient in this process (McWhinney 1989:46).

As McWhinney points out himself, this model provides a good fit with certain categories of diseases, and especially those that dominated medical practice in the 19th Century, such as infectious diseases and nutritional deficiencies. But in other settings, and very notably in contemporary primary care, the deficiencies of the Old scientific paradigm are hard to ignore (McWhinney 1989). And McWhinney was bold enough already in 1989 to propose a *New Paradigm*, where:

> Disease is not separated from the person, or the person from his or her environment. Conventional disease categories are still used as a frame of reference, but always in context. All illnesses have both mental and physical components. All have multiple causes, although it may be useful to focus therapy on a single causal chain. Causation acts not only in a linear but also in a reciprocal function. The relationship between doctor and patient has a profound effect on the illness and its course (McWhinney 1989:56).

Final reflection: Towards a medical renaissance?

What McWhinney is indirectly suggesting with his *new paradigm*, is that Hippocrates´ approach to 'the vulnerable human condition' was basically a scientifically sound one. And, although Hippocrates´ way of thinking about nature might be considered as 'primitive biomedicine', his overall 'way of knowing' about disease, suffering and healing was qualitatively different and in some respects more advanced than ours. As Heidegger suggested in *The question concerning technology* (see 2.4.2), we might profit from looking better into ancient Greek philosophy. What we need, is perhaps *a medical renaissance*?[162]

[162] Interestingly, the 12th regional European conference for the world association of family doctors (WONCA) which is to be held in Florence (the centrum of the Italian renaissance around 1500) in 2006, has the slogan *Towards medical renaissance. Bridging the gap between biology and the humanities*. (www.woncaeurope2006.org/home/index.htm).

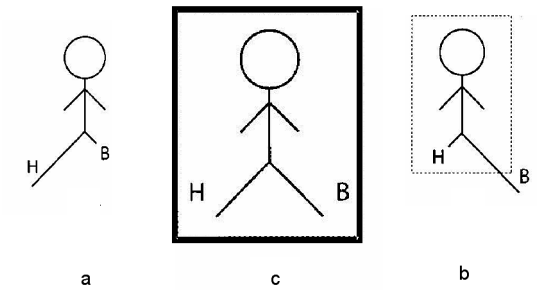

Figure 12.2

a: Hippocratic medicine was mainly a humanistic discipline (H) influenced by a newborn interest for what we today consider as the natural sciences (B).
b: In contemporary medicine, the B leg may have become too long, seen in comparison to its H counterpart, and perhaps also if seen in relation to the practical possibilities and resources (marked with a frame).
c: A better balance between H and B is needed for medicine to progress in a sustainable and responsible fashion, within reasonable limits of resource use (the figure is adopted from Hetlevik 2004).

END

12.3 APPENDIX. Ultrasound screening for Down syndrome: a brief historical overview

> *Those planning a pregnancy and the professionals who help them all need to ensure that relevant risks are addressed using evidence-based methods*
>
> *– Sandy Raeburn, BMJ 2000*

Human procreation is deeply embedded in a social, political and cultural context (Oakley 1993; Parens and Asch 2000; Solberg 2003). The use of medical technology in the area of obstetrics and fetal medicine will therefore always be intertwined with fundamental aspects of human existence and experience. Prenatal testing in general, and ultrasound screening of pregnancy in particular, have been debated topics in society at large, involving academics far beyond medicine. Few health care workers outside the narrow medical expert communities have insight into the complicated issue of prenatal screening and diagnostic tests. In fact, most medical doctors appear quite reluctant to participate in the debate on prenatal testing (Klein 1998; Getz 2001). In connection with the preparation of Paper I in this thesis, I explored the technicalities and ethical dilemmas related to prenatal testing to considerable depth (Getz 2002). The present chapter contains background information with relevance to Paper I of this thesis.

The history of ultrasonography in obstetrics dates back to Glasgow in the 1950s where ultrasound was being intensively used in relation to heavy engineering projects. By the late 1970s, ultrasound had become a common method of fetal surveillance in many countries. The first controlled scientific study of obstetric ultrasound was however not published until 1980, which was the year when it was suggested that ultrasound should become an integrated part of routine antenatal care on an international basis (Oakley 1986).

Since the second half of the 1980s, an ultrasound examination has been routinely offered to all pregnant women in second trimester of pregnancy (week 17-20) in many Western countries. Whilst ultrasound examination has become an indispensable tool in situations where clinical problems arise or are anticipated, the benefit of ultrasound screening remained uncertain and subject to much controversy, involving also the Norwegian expert community (Eik-Nes et al. 2000).[163] Most expectant parents have however accepted, and to an increasing extent asked for, ultrasound examinations for purposes such as dating the pregnancy, receiving general reassurance, and 'seeing' the baby (see references in Paper I). Ultrasound is generally considered to be a biologically safe procedure, but a potential for subtle harmful effects cannot be definitely excluded (Westin and Bakketeig 2003).

The scope and aims of prenatal ultrasound screening have undergone significant changes since it was introduced in the 1980s. The test originally aimed at *reducing*

[163] In 1995, this was evident at the Norwegian consensus conference on the use of ultrasound in pregnancy in 1995. See: Bruk av ultralyd i svangerskapet. Konsensuskonferanse. Rapport Nr 9 fra Komiteen for medisinsk teknologivurdering. Norges forskningsråd: Oslo, 1995. (Proceedings from the Norwegian consensus conference on use of ultrasound in pregnancy, 1995).

obstetric risk, i.e. enhancing medical safety for mother and child, by correcting gestational age, locating the placenta and diagnosing twin pregnancies. As imaging technology developed, *diagnosis of visible, anatomical abnormalities* became possible. Diagnoses of major anomalies such as a missing brain have been relatively precise from the start. Clinical uncertainty and counselling dilemmas have however arisen in relation to more subtle findings. This problem was initially high-lighted in a small case series published in Lancet in 1985 (Griffiths 1985, see Paper I). As a result of clinical training and increasing expertise, some uncertainties would gradually be resolved, but then new uncertainties arose instead. In a 1987 Lancet debate paper, an experienced ultrasound examiner stated (Furness 1987, see paper I):

> Rapid technological advance means that each machine update shows the observer features never recognised before, necessitating a reappraisal of the range of normal at each stage of pregnancy. (…) It also means that ultrasound publications lag substantially behind current knowledge and practice, and exchange of information tends to be anecdotal.

From around 1990, there was a rapidly increasing medical interest in identifying fetuses at *increased risk for chromosomal aberrations*, particularly Down syndrome, by ultrasound in the second trimester of pregnancy. Most fetuses with Down syndrome show no distinct anatomical anomalies, but they often exhibit subtle features in the grey zone between the 'normal' and the 'pathological'. Attempts to "pin-point" subtle anatomical indicators of an increased risk for Down syndrome had started in the 1980s, but after 1990 they became more systematic and widespread (see Paper I). The minor anatomical changes were now ever more often referred to as *soft markers* in the scientific literature (illustrations of two soft markers can be found in Paper I).

The ethical dimensions of ultrasound screening in pregnancy are complex. In terms of informed consent, the different tests that together constitute a state-of-the-art routine prenatal ultrasound examination come as an 'all-or-none' package. The tests however have fundamentally different motives and moral implications. Few people are likely to reject an examination which promises to increase safety for mother and child-to-be. It also appears that many expectant parents prefer to be informed about life threatening or lethal anomalies in the fetus. Screening for disabling but not lethal chromosomal aberrations for which there is no medical 'treatment' other than the option to terminate the pregnancy is a more demanding issue to consider - both technically and ethically. As outlined in Paper I, expectant parents have reported that information about an increased risk for Down syndrome in their child-to-be can be emotionally overwhelming (Baillie 2000, see Paper I). The monitor screen will however reveal information related to all three agendas simultaneously. If your want to 'see' your baby, you also consent to the rest.

In April 1997, a British professor of obstetrics wrote an editorial to the BMJ warning that he believed detection of ultrasonographic soft markers of fetal chromosomal defects could do more harm than good in routine clinical practice (Whittle 1997, see Paper I). Reading this editorial was among the events that triggered my personal interest for the subject. Paper I in this thesis documents the chronological development of

and analyses the impact of medical activity related to the soft markers, from its beginning in the mid 1980s till its culmination in the late 1990s. The manuscript was first submitted to *Social Science and Medicine* in the fall of year 2000. It concluded that during the last decade, the interest in soft markers for fetal chromosomal aberrations appeared to have caused considerable harm -- in the form of parental distress and the loss of countless wanted, healthy children-to-be in the wake of invasive diagnostic testing performed to resolve uncertainty generated by premature application of medical technology in a routine setting. The four anonymous reviewers, all described to us authors as experts in prenatal diagnosis, were not convinced that our analysis was valid. At this critical moment, a meta-analysis of the clinical-epidemiological aspects of the soft markers was published in the *Journal of the American Medical Association (JAMA)*. On the basis of mathematical calculations, the authors presented the same conclusion as we did.

Many of the world's top experts in prenatal ultrasound are situated in Britain. In the UK, screening for anatomical soft markers by second trimester ultrasound was rapidly discouraged after the publication of the meta-analysis in *JAMA* (Reported by the West Midlands perinatal institute 2002). In the more complex healthcare environment of the USA, counselling dilemmas related to second trimester soft markers were still a hot topic at an expert meeting in 2004 which was attended by a correspondent from the JAMA. The correspondent asked one of the world's most renowned experts in the field of soft markers (Hampton 2004):

> "But physicians cannot help but see these markers during an ultrasound. So what should they tell the parents?"
>
> "By all means, provide information", says [expert epidemiologists name]. "It's not clear to me though, what information you're going to provide."

In 1986, professor in sociology Ann Oakley summed up an investigation of the history of ultrasonography in obstetrics (see chapter 2.4.6) as follows: "I have drawn out the historical lesson that there is not nearly enough scientific evaluation of techniques that enter clinical practice" (Oakley 1986). This was at the start of the period that was to be characterised by "the rise and fall" of second trimester soft markers.

What is the current state of affairs related to Down syndrome screening by ultrasound when this thesis goes to print? Screening is more widespread than ever, but the context has changed: During the 1990s, as a direct spin-off effect of the trial and error efforts to find useful soft markers in the context of *second* trimester, British researchers discovered that one of the soft markers that did not work well in the second trimester appeared useful in the *first* trimester of pregnancy. The foundation for a screening test called 'the 11-14 week scan' was thereby laid. And as opposed to second trimester ultrasound screening, this *early ultrasound screening* has been *explicitly* developed and promoted as a screening test for Down syndrome. The main parameter that is measured is called nuchal translucency (NT), the maximum thickness of the subcutaneous space between the skin and the soft tissues overlying the fetal cervical spine (see illustration in paper I). Thickened NT is a relatively sensitive and specific indicator of chromosomal aber-

rations, but it may also be indicative of other kinds of fetal abnormality such as heart defects. The NT-screening test can be further enhanced if ultrasound measurements are combined with the results of maternal serum tests (so-called combined screening). Women who are test positive (the estimated risk for Down syndrome being higher than 1:300) are offered invasive diagnostic testing. Invasive testing involves about 1% risk for losing the pregnancy.

A recent multi-centre study of first trimester combined screening for trisomy 21 in the United Kingdom involved almost 76 000 pregnancies. The overall detection rate for Down syndrome was 90%, with a false-positive rate of 5% (Nicolaides et al 2005). Several fetal medicine experts and statisticians are currently involved in theoretical modelling of more complex Down syndrome screening programmes with the aim to increase the precision of the technology further (Cicero 2003, Nicolaides 2005).

The medical community has now succeeded in developing a technology that can prevent nine out of ten people with Down syndrome from being born. The risk of losing an unaffected pregnancy due to invasive testing is much lower in the context of early ultrasound screening than it used to be in the context of amniocentesis based on maternal age (Getz 2002). This technically safer approach however implies that *every pregnancy*, irrespective of maternal age or previous birth history, must be regarded as *at risk* until screening has been performed.

Early ultrasound screening is currently being implemented in many countries. In 2003, the National Institute of Clinical Excellence (NICE) stated the it is an aim to offer combined screening to all pregnant women in the UK by the year 2007 (NHS guidelines, issued Oct 6th 2003). In Norway where the policy in relation to prenatal diagnosis has been conservative, at least by comparison with the other Nordic countries and the UK (Getz 2002), the prospect of systematic early ultrasound screening has periodically lead to considerable debate, mostly in the media (Solberg 2003). In Iceland, early ultrasound examinations are increasingly common, but a formal screening programme has not been implemented. Opinion leaders in the primary health care system have been reluctant to take part in screening ever since the idea was launched in 2000. The fetal medicine expert community has twice (last time in May 2005) presented almost complete drafts of public screening information material to the Icelandic experts of primary health care. The drafts have been rejected on the ground that they have focused almost exclusively on pathological descriptions and characteristics of the medical tests in question, whilst avoiding to address the moral questions which are bound to arise in relation to a technology which is developed with the specific aim to sort out lives that are not, by medical standards, considered as worthy of living.

The first lawsuit has recently been filed in Denmark against an ultrasound examiner after the 'wrongful' birth of a child with Down syndrome after early ultrasound screening.[164] A formal screening programme had then existed in the country for about a year. So, once the technology which aims to prevent the birth of children with Down syndrome has reached a certain level of sophistication, a next 'generation' of technology-

[164] see www.politiken.dk/VisArtikel.iasp?PageID=401892.

related moral dilemmas emerges: people who have come to realise that we live in a risk society (Beck 1992), and have learnt to take the necessary precautions as responsible citizens, are now likely to look at the face of a young child with Down syndrome and wonder who is to blame (Marteau and Drake 1995). Was it the mother who did not take the test, or was it medical technology that failed?

END

12.4 APPENDIX. Cardiovascular disease prevention in clinical practice: historical time-line

As I worked with papers II, IV and V in this thesis, I decided I ought to get a better overview of the historical origins of our contemporary way of handling cardiovascular disease prevention. I took notes about the subject, and this resulted in a historical time-line. The list contains events and milestones that I see as important and interesting, directly or indirectly, in relation to theory, research and practice in the area of CVD prevention. I particularly emphasise the management of hypertension, elevated cholesterol, and the paradigm of "combined cardiovascular disease risk estimations." I also take notice of emerging psycho-social risk factors that are not (as yet) included in the contemporary "EBM" approach to CVD.

I have not penetrated discussions and controversies concerning exactly what drugs to use to achieve treatment targets regarding the risks factors, except that I briefly mention the most recent debate regarding the use of thiazides and beta blockers, versus newer and more expensive drugs.

The topic of cardiovascular disease prevention and its history is a vast subject. I deliberately focus on some general trends, from a relative distance and a certain angle. This time line should be considered as a draft, and not as a final, authoritative document. The timeline may contain errors, as well as omissions of relevant milestones that I am simply not aware of.

SELECTED HISTORICAL EVENTS AND TRENDS

1827: Recognition that many patients with renal disease have diffuse vascular disease, kidney disease, and cardiac hypertrophy (the study does not address blood pressure).
Ref: Bright R. Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine. Guy's Hos Rep 1836;1:338-400, see Ventura et al. 2001.

1896: Riva-Rocci invents the **sphygmomanometer** (the device for blood pressure measurement, in principle as we know it today), enabling easy and non-invasive measurement of blood pressure.

1911-13: **Early studies describing cases of hypertension.**
Ref: Allbutt TC. An address on arteriosclerosis of the kidneys. BMJ 1911;1:853-922, Janeway TC. Nephritic hypertension: clinical and experimental studies. Am J Med Sci 1913;145:625-35, both referred in Ventura et al. 2001.

1912: Measurement of blood pressure becomes standard procedure at admittance to the Massachusetts General Hospital in the USA (See Porter 1997: 344).

1914: German researchers describe the features of **"red" hypertension** (essential hypertension with good prognosis) as opposed to **"pale" hypertension** (with chronic nephritis, retinal damage and a poor prognosis).

Ref: Volhard F Fahr T. Die Brightsche Nierenkrankheit: Klinik, Pathologie und Atlas. Berlin: Julius Springer, 1914. See Ventura et al. 2001.

1925: The publication of the first English **case report of "sudden death after a heart attack with severe crushing chest pain."** Source: James Le Fanu's book *The rise and fall of modern medicine* (1999:323). As noted in relation to the clinical topic of CVD in the theoretical introduction to this thesis, we are here at the early beginning of what has been called "a modern epidemic of CVD", see figures in chapter 3.2.

1928: The **term "malignant hypertension" appears in the English literature**, in connection with a case series including 14 patients who survived 1-44 months.
Ref: Keith NM et al. The syndrome of malignant hypertension. Arch Int Med 1928;41: 141-8, see Ventura et al. 2001.

1930s and 1940s: Period of authoritative recommendation that "…hypertension might be an important compensatory mechanism, which we should not tamper with even if we know how to control it."
Example: White PD. Hypertensive heart disease. In: Hypotension in heart disease. NY: Macmillian 1932, p 391-409, see reference list in Ventura et al. 2001.

1934: Philosopher of science Karl Popper publishes the book *Logik der Forschung* (English: Logic of scientific discovery, 1959 – it is still a classic). **Popper advocated falsifiability as the criterion of demarcation for science.** The tradition for formulation, testing, and rejection of null hypotheses now begins to develop.

1940s and 50s: **"Desperate" treatment regimens for accelerated/malignant hypertension.** Severe blood pressure elevation associated with subjective symptoms and rapid, widespread organ damage (generally with a fatal outcome) is treated with drastic diets, major surgery, pyrogens and various drugs. All these heroic regimens have major side effects.
A good review paper on the topic of hypertension treatment in these days is: Ventura HO, Mehra MR, Messerli FH. Desperate diseases, desperate measures: tackling malignant hypertension in the 1950s. Am Heart J. 2001 Aug;142(2):197-203.

1940s: US president **Franklin Delano Roosevelt (1882-1945) had progressing hypertension** from around 1937. He developed left ventricular hypertrophy, congestive heart failure, multiple lacunar infarcts, renal failure, and died of a cerebral haemorrhage aged 63. Roosevelt was "grossly fatigued… his colour very poor" when attending the Yalta conference in February 1945, only eight weeks before he died. Roosevelt's physician, Dr. Howard Bruenn, has written that although FDR suffered from high blood pressure, there was no evidence that his health impaired his judgment at Yalta. Not everybody believes that Roosevelts judgement was intact, however (le Fanu 1999:130).

1948: **The Framingham heart study is established**
The Framingham study included about 5000 individuals aged 30-74 years from the small town Framingham outside Boston, USA. The Framingham Offspring Study (1971) later came to succeed the original cohort study. A third cohort was included in

2002. The epidemiological quality of the original Framingham study has been criticised for various reasons; a topic I will not go into here. The Framingham heart study has resulted in more than 1200 scientific papers. A timeline of Framingham "milestones" can be found at:
www.nhlbi.nih.gov/about/framingham/timeline.htm.

1950: The ability of Aspirin (synthesized in 1897) to prevent blood clotting is noted by a U.S. family physician named Lawrence Craven. He suggests that aspirin might therefore reduce the risk of coronary thrombosis, and publishes his hypothesis (in Annals of Western Medicine and Surgery 1950;4:95-9, see also le Fanu 1999 who describes this story). Nothing happens in the wake of this publication, however. See next milestone on "aspirin" in 1971.

1950s and 60s: The famous **"Platt versus Pickering" debate on the nature of hypertension.** Debate issue: is hypertension a distinct disease entity (ad held by Platt), or are people with hypertension simply located on the tail of the blood pressure normal distribution curve (as maintained by Pickering).
Ref: Swales JD. *Platt versus Pickering. An Episode in Recent Medical History*. London: The Keynes Press, 1985.

1950: **Two general milestones in epidemiology announce a methodologcial 'paradigm shift':**
1) the randomised controlled drug trial (treatment of tuberculosis, BMJ 1950;Nov 11:1074-85), and
2) epidemiological method enabling identification of disease risk factors (the documentation that smoking causes lung cancer in BMJ 1950;Sept 30: 740-9).
For discussions of the enormous implications of these methodological advances, see le Fanu (1999) and Doll R: Sir Austin Bradford Hill and the progress of medical science. BMJ 1992;305:1521-6.

1951-2: US Pentagon-associated pathologists perform **autopsies on US soldiers** who fall in the Korean war and discover that extensive atherosclerotic disease can frequently be present in healthy men from the age of 20 – this was until now an unknown fact.

1955: **Open heart surgery** is performed for the first time (this is among the 12 milestones in le Fanu's (1999) list of medical triumphs in the post-war era).

1955: **US President Dwight D. Eisenhower (1890-1969) has a "billion-dollar heart attack"** whilst playing golf. He was later the same day treated by his personal physician in his home with amyl nitrate to sniff, and sequentially injected papavarine and morphine. The president then fell asleep, but as he had not recovered when he awakened a few hours later, an electrocardiograph was brought to his house. An anterolateral myocardial infarction was confirmed. Eisenhower was then admitted to an army hospital, 24 hours after the attack. There, he dwelled in an oxygen tent and received heparin i.v. The news of the infarction had a dramatic effect on the country's financial market; the Dow Jones dropped by 6%, a decline that had not been seen since 1929. One of USA's most famous cardiologists attended Eisenhower as a consultant, and a

month later he summed up current knowledge regarding risk of myocardial infarctions. Many of the risk factors are those we know today, but tobacco use was mentioned as something quite unimportant, although in need of further appraisal. (Eisenhower was a heavy smoker.) Eisenhower recovered well from his infarction and was back playing golf five months later, but did endure a period of anxiety and depression after the event. He was re-elected in 1956, then suffered a minor stroke, but completed his second term as a president. In 1965, he had another serious MI and retired from public affairs. From his first infarction in 1955 until his death at the age of 78, Eisenhower reportedly had at least seven MIs and several cardiac arrests. He was one of the first patients to profit from the defibrillator, introduced in 1962. Ref: Messerli F et al. Eisenhower's billion-dollar heart attack – 50 years later. N Engl J Med 2005;353:1205-7.

1958-61: Open studies document **effectiveness of treatment of malignant hypertension.**

1958: **Thiazide antihypertensive diuretic drugs are introduced.** This is a first step towards introducing generally safe and tolerable antihypertensive drugs.
Ref: Freis ED et al. JAMA 1958;166:137-40.

1960: **Smoking is found to increase the risk of heart disease** in the context of the Framingham heart study.

1960: The formal "coronary care unit" is introduced in hospitals.

1960-1: **Hypertension, elevated cholesterol and smoking are defined as the main risk factors for ischemic heart disease in the Framingham heart study.**

1960s: Mortality from stroke starts to decline in Norway in the 1950s both for men and women aged 55-64 years, and one decade later for men and women aged 65-74 years; i.e. before hypertension treatment is introduced on a large scale in the health care system.
Ref: Ellekjær H. Epidemiological studies of stroke in a Norwegian population. Incidence, risk factors and prognosis. Dissertation. Trondheim: Tapir, 2000.

1962: A WHO Technical Report Series (No 231) draws attention to the importance of controlling arterial hypertension in relation to prevention of ischemic heart disease

1962: The direct current-defibrillator is introduced.

1962: Philosopher of science Thomas Kuhn publishes his book *On the Structure of Scientific Revolutions* (Kuhn 1962), introducing the notions "scientific paradigm", "normal science," "anomalies" and "paradigm shifts." This work is briefly outlined in Appendix 2.

1964: **The first controlled clinical drug trial of non-malignant essential hypertension shows that treatment prevents strokes.** The trial included 61 patients under

the age of 60.[165] Inclusion criteria were a sustained DBP ≥110 mmHg in an otherwise asymptomatic individual with no objective signs of organ damage. This trial appears on le Fanu's (1999) milestone list under the title "The triumph of prevention – the case of strokes". The idea of recommending potentially life-long medical intervention to individuals who were free from both subjective symptoms and objective signs of organs damage when therapy is instituted, motivated by the presence of what could be considered *a disease risk factor only*, represents something completely new in medicine.
Original reference: Hamilton M, Thomson EN. The role of blood pressure control in preventing complications of hypertension. The Lancet 1964;Vol I, pp. 235-9.
See also: Beevers DG. The 40th anniversary of the publication in 1964 of the first trial of the treatment of uncomplicated, severe hypertension by Hamilton, Thompson and Wisniewski. J of Human Hypertension 2004;18:831-833.

1965: Sir Austin Bradford-Hill presents a seminal paper on **criteria for causality, as viewed in an epidemiological context**. The criteria were: Strength of association; Consistency of association; Specificity of association; Temporality – i.e. exposure must precede outcome; Biological gradient; Biological plausibility and Coherence with other facts; and – if relevant – Possible to confirm by Experimentation; Analogy (i.e. recognition of resembling patterns, such as the educated guess that a new birth defect may be caused by exposure to some drug effect in utero).
Ref: Bradford-Hill A. The environment and disease: Association or causation? Proc R Soc Med 1965;58:295-300.

1967: **The first Whitehall study is established**, including about 18 000 men in the UK Civil service. This study came to document that men in the lowest employment grades were much more likely to die prematurely than men in the highest grades. The Whitehall II study was subsequently set up in 1985 to determine what underlies this social gradient in death and disease, and to include women. The Whitehall studies are mentioned in the theoretical introduction to this thesis, and some of the research findings will be chronologically listed below.

1967 & 1970: **"The veteran studies" provide further evidence that treatment of hypertension decreases CVD morbidity and mortality.**
References: Veterans Administration Cooperation Study Group on Antihypertensive agents. Effect of treatment on morbidity in hypertension.
I. Results in patients with diastolic blood pressure averaging 115-129 mm Hg. JAMA 1967; 202:1028-34.
II. Results in patients with mild-moderate hypertension, i.e. diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 1970;213:1143-52.

[165] The study recruited one group who received drug treatment (20 females and 10 males), and a control group who received no medical intervention (19 females and 12 males). Allocation to the groups was not strictly randomised. The nature and intensity of the drug intervention varied considerably among the treated subjects. Details are not presented in the paper; it is however stated that a higher proportion of males than females achieved 'good' blood pressure control, and that this was potentially due to "prejudice in favour of therapy in the male". A total of five cardiovascular disease complications (events) occurred in the treatment arm - all of them in female subjects. 16 events occurred in the control arm. The authors´ main conclusion was: "It is recommend that males under the age of 60 and with severe sustained hypertension require treatment on this account even though the disorder is symptomless and uncomplicated."

The 1960s: **Beta-blocker drugs are introduced.** Treatment of asymptomatic individuals with hypertension could thereby be regarded an even more realistic possibility.

1970s: A **decrease in the epidemic of ischemic heart disease begins** in the Western world, see the figures in chapter 3.2.

1971: British biochemist (and later Nobel Prize laureate) John Vane documents the biochemical pathway underlying aspirin's effects, by inhibiting prostaglandin synthesis in blood platelets. Reference: Nature: New Biology 1971;231:230-5. (see le Fanu 1999:469).

1969-1975: Harvard pathologist Mc Cully and co-workers. launch "The homocysteine theory of arteriosclerosis," see for instance Atherosclerosis 1975 Sep-Oct;22(2):215-27. The hypothesis was first rejected, and Mc Cully lost his position at Harvard, unable to find another academic position. It has been argued that the resistance against the homocysteine theory was due to its perceived conflict with the cholesterol theory of heart disease (see Podell RN Medical Hypothesis 2003;61:340-5).

1976: Ivan Illich publishes his book "*Medical nemesis. Limits to medicine*" (Illich 1976). Here, he introduces the concept of medically induced harm, iatrogenesis, on three levels: clinical, social, and cultural iatrogenesis (further described in chapter 2.3.4).

1976: An increased risk for heart disease after female menopause is documented in the Framingham heart study.

1977: **The First U.S. Joint National Committee (JNC) Reports on blood pressure are issued.** Recommendation: Treat if BP remains > 160/95, in particular in people under 50 years.

1978: **Psychosocial factors are found to affect heart disease** in the Framingham study

1978: WHO (Technical Report Series, 628, written by the WHO expert committee on hypertension) defines "Normal BP" ≤140/90, "Borderline BP" = 140-160/90-95, and "Hypertension" as BP ≥160/95.

1970s: Trials of primary and secondary prevention of ischemic heart disease using the cholesterol lowering drugs clofibrate, nicotinic acid, gemfibrozil, leading to up to 20% reduction in coronary heart disease events, but no reduction in mortality.

1978: Haynes, Sackett et al. publish a paper where they demonstrate that "Blood pressure labelling" increases absenteeism from work. Ref: Haynes RB, Sackett DL, Taylor DW, Gibson ES, Johnson AL. Increased absenteeism from work after detection and labelling of hypertensive patients. N Engl J Med. 1978;299:741-4.

1979: Stott and Davis present their seminal paper on "The exceptional potential in

each primary care consultation", introducing 'opportunistic health promotion' as part of the good standard consultation (point of departure for Paper III in this thesis).

From the 1970s into the 1990s: Several studies find associations between so-called "Type A" personality behaviour, depression and anxiety, psychosocial work characteristics, social network and social support and coronary heart disease. See an overview of this work in a review paper by Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ 1999;318:1460-7.

1950-70s: Widespread public **campaigns with the message that "the Western diet with its high proportion of saturated (animal) fat is highly pathogenetic."** This particular epoch is reviewed in a critical 1977 paper in the The New England Journal of Medicine titled "Diet-Heart: End of en era" (Mann GV. NEJM 1977; Sept 22: 644-50). The era began in the 1950s after a method for characterising the blood lipoproteins had been invented. One of the main researchers in this area was Angel Keys who published extensively and used data from World Health tabulations to conclude that in six countries, experience with coronary heart disease was correlated with available food fat. In the NEJM, Mann writes: "In a few years, some combination of urgent need of health agencies, oil-food companies and ambitious scientists had transformed the fragile [diet-heart] hypothesis into a dogma (…) Physicians were overwhelmed by this assault. (…) The diet-heart-propaganda was escalated by a succession of recommendations from the American heart Association. (…) To be a dissenter was to be unfunded because the peer-review system rewards conformity and excludes criticism." The disputes surrounding the "high fat Western diet" theory are discussed in le Fanu's book (1999) and also in le Fanu J. The case of the missing data. BMJ 2002;325:1490-3.

1982-3: **Two famous lifestyle intervention randomised controlled trials:**
– the "MrFit" (Multiple Risk Factor intervention) trial in USA - sponsored by the National Heart, Lung and Blood institute and recruiting 12.866 men at high risk (see JAMA 1982;248:1465-77), and
– "WHO multi-factorial trial" (conducted in Europe and recruiting 49.871 men (see Eur Heart J 1983;4:141-7).
Both studies showed very limited if any benefit in terms of effect on hard endpoints of intensive intervention involving antihypertensive medication, life style advice with lipid-lowering diet and non-smoking advice.

1984: The **LRC** (Lipid Research Council) trial. The cholesterol lowering drug cholestyramine is here shown to reduce deaths from heart disease in middle-aged men with cholesterol >6,9mmol/l or LDL >5,9 mmol/l. (Ref: The Lipid Research Clinics Coronary Primary Prevention (LRC-CPPT) Trial. JAMA 1984;251:351-64, and 365-74). Some effect was found on CVD endpoints, but no effect was documented on total mortality. An insignificant increase was found in deaths from violent causes in the intervention group. Cholestyramine is a bile acid reuptake inhibitor that increases the excretion of bile acids in the faeces. Treatment appeared to be safe but associated with considerable gastrointestinal side effects. The LRC trial was discussed in a Lancet editorial (Lancet, Feb 11th 1984) titled "Is reduction of blood cholesterol effective?" It

concludes that the sum of evidence that reducing cholesterol with medication reduces heart disease in people with high risk is now convincing, and that "Despite the scientific uncertainties of extrapolation, the benefits that emerged for those at highest risk give further support for the case for cholesterol reduction in the population as a whole". Massive campaigns to "know your cholesterol number" and promotion of drug treatment to lower cholesterol start in the wake of this trial, particularly in the USA.

1980s: Several studies indicate that pharmacological treatment of moderate and mild hypertension can reduce morbidity from CVD. One such study was the 1985 MRC (Medical Research Council) trial of treatment of mild hypertension (Br Med J (Clin Res Ed) 1985 Jul 13;29197-104). It was the largest study on blood pressure intervention ever done. It documented that treatment of mild hypertension by thiazide or beta-blockers reduced stroke rates by 46% if measured as relative risk reduction (absolute risk was reduced from 2,6 to 1,4 per 1000 patient years). Treatment did not significantly affect overall rates of coronary events, and mortality from all causes was not affected. There were in total 248 deaths in the treated group and 253 in the placebo group (rates 5.8 and 5.9 per 1000 patient years respectively).

1985: Thrombolysis after myocardial infarctions is introduced.

1985: **The second Whitehall study is established**, including more than 10.000 administrative employees, men and women. The aim is to investigate the social gradient present in relation to all major causes of disease, documented in the Whitehall I study. The crucial research question is: "How do human values translate into pathology?" Some findings with relevance to this thesis will appear below (year 2002-5). See also Chapter 2.1.4 in this thesis and the homepage of the Whitehall II study (http://www.ucl.ac.uk/whitehallII/).

1986: **The US CARDIA (Coronary Artery Risk Development in Young Adults) study** is established. It examines how heart disease develops. From 1986 it included a group of 5115 black and white men and women aged 18-30 years. The participants were selected so that there would be approximately the same number of people in subgroups of race, gender, education and age (18-24 and 25-30). The participants were asked to participate in follow-up examinations at year 2, 5, 7, 10, 15, and 20 (which is now in 2005-6). A majority of the group has been examined at each of the follow-up examinations, response rates have been 90-74%.
See (www.cardia.dopm.uab.edu/index.htm).

1987: The **Helsinki heart study** is published. It involved 4081 healthy men with a mean age of 47 years and a total cholesterol as high as 7,5 mmol/l. It showed that cholesterol reduction with gemfibrozil (a fibrate) reduces the incidence of coronary heart disease (RRR 26%) in men with dyslipidemia. No effect was observed on total mortality. The Number Needed to Treat (NNT) in this study is 84 healthy men treated for 5 years to prevent one non-fatal myocardial infarction. Ref: Frick MH et al., N Engl J Med 1987;317:1237-45.

1987: The US National Heart, Lung and Blood Institute promotes cholesterol-testing for all adults.

1987: **The first statin drug is introduced on the market** (lovastatin, Mevacor). Statins are drugs which inhibit the enzyme HMG-CoA reductase and lower cholesterol synthesis in the body.

1988: A hypothesis that chlamydia infection (TWAR) may cause chronic coronary heart disease is launched. Ref: Saikku et al. Lancet 1988;2:983-6.

1987-93: Several expert panels in the USA and Europe advocate dietary changes and if necessary, drugs to reduce LDL concentration, especially in patients with coronary heart disease. By this time, no trial has convincingly shown that lowering of cholesterol prolongs life. A 1990 review in the BMJ concluded that "the failure of cholesterol lowering to affect *overall survival* justifies a more cautious appraisal of the probable benefits of reducing cholesterol concentrations in the general population." The authors are concerned that the reduction in CVD mortality was offset by an increase in death from other causes. Ref: Muldoon MF et al. BMJ 1990;301:309-14.

1989: Thomas Moore publishes a book called "Heart failure," (Random House, 1989) where he shows how the National Heart Lung and Blood Institute, the earliest proponents of cholesterol reduction, has been selective about the research that formed the basis of their treatment guidelines. A summary of the book appears in the journal Atlantic Monthly (1989;264:no 3) under the title "The Cholesterol Myth."

1990: High cholesterol is now regarded by many authorities as *the* main cause of coronary atherosclerosis. See for instance: Gotto AM et al. The cholesterol facts. Circulation 1990;81:1721-33.

1991: EXCEL, the first RCT which addressed the efficacy and safety of lovastatin is published. (Bradford RH et al., Arch Int Med 1991;151:43-9). The study included 8245 patients with moderate hypercholesterolemia. The abstract states that statins effectively and safely reduce lipid levels (i.e. is effective on surrogate end points).

1991: The SHEP study (Systolic Hypertension in the Elderly Program). Until the early 1990s, it was considered that high blood pressure in elderly people (over 65-70 years) should not be treated, unless the patient had angina or heart failure that could become symptomatically better by use of antihypertensive medication. SHEP was a double blind RCT involving about 4700 patients > 60 years with isolated systolic hypertension (SBP in the range 160-220mmHg and DBP<90mmHg). It tested the diuretic chlorthalidone versus placebo over 4,5 years. The results indicate that treatment of isolated systolic hypertension reduces strokes. JAMA 1991;265:3255-64.

1991: **The STOP study** (Swedish Trial in Old Patients with Hypertension) was a double blind RCT involving around 1600 persons 70-84 years. It tested thiazides, beta blockers or both versus placebo. Inclusion criteria were BP >180-230/90, or diastolic pressure >105mmHg. The study was stopped prematurely (truncated) after 2.1 year. This is the first BP intervention study to document effect of BP treatment on total mortality. Relative risk reduction (RRR) was 43%, Number Needed to Treat (NNT) was 30 individuals for 2 years. (See Lancet 1991;338:1281-5).

1991: **The first Framingham Heart Study Prediction Score Algorithm is launched.** The Framingham risk-score system estimates risk for fatal and non-fatal cardiovascular disease events in men and women.

1992: Geoffrey Rose, arguably the most influential epidemiologist ever in the field of cardiovascular disease prevention, publishes his influential book "The strategy of preventive medicine" (Oxford: Oxford University Press, 1992). Here, Rose outlines two different approaches in preventive medicine: The population approach (mass strategy) on the one hand, and interventions in relation to individuals at particularly high risk (high-risk strategy) on the other.

1992: The previously unpopular "homocysteine theory" of CVD (see 1969-75) has a comeback in mainstream medicine. Ref: Stampfer et al. A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. JAMA 1992;268:877-81.

1991-2003: **"On the favourable effects of diet modification on CVD"**: Some highly influential papers are published between 1991 and 2003 by RB Singh and co-workers, showing that an "Indo-Mediterranean" diet can have a clinically significant cardioprotective effect in relation to CVD. In one study for instance, it appeared that after a MI, one year of a low fat, fibre rich diet almost halved the risk of death from all causes.
See for instance Singh RB et al: Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up. BMJ 1992 Apr 18;304(6833):1015-9. Singh et al. continue to publish papers demonstrating similar effects, including a paper in the Lancet in 2002. Singh's data were in 2005 considered by the BMJ and the Lancet as probably fabricated or falsified (see year 2005).

1992-7: **Establishment of the tradition called "Evidence based medicine".**
See chapter 2.2.7 in this thesis (including key references).

1993: **The Cochrane Collaboration (CC) is established**, named after epidemiologist Archie Cochrane (1909-1988), a British medical researcher who contributed much to the development of epidemiology as a science. The CC is an international, non-profit, independent organisation, established to ensure that up-to-date, accurate information about the effects of healthcare interventions is readily available worldwide.
See www.cochrane.org.

1993: The **JNC V guidelines** are launched. Hypertension is now considered a major risk factor for which treatment is recommended if **BP > 140/90** mmHg.
A good review paper on hypertension treatment up to this point in time is
Moser M. Evolution of the treatment of hypertension from the 1940s to JNC V. Am J Hypertension 1997;10:2S-8S.

1994: Realising that commercial interests may strongly affect researchers' scientific opinions, the British Medical Journal introduces a "Conflicts of interest" statements for authors. (The term is later changed to competing interests). Other medical journals follow suit in the years to come.

1994: **The 4S study** (Scandinavian Simvastatin Survival Study) included 4444 men and women 35-70 years with previous myocardial infarction or angina, i.e. secondary prevention. The cholesterol level among participants was in the range of 5,5-8,0 mmol/l. This study is the first to document efficacy of secondary prevention of coronary heart disease with a statin. **For the first time, intervention to reduce cholesterol showed a favourable effect on total mortality** (RRR 30%, ARR 3,2% over 5,4 years). The reduction of major coronary events was ARR 8,6% in 5,4 years. The effect on major events was greater in men than in women, and total mortality was not significantly reduced in women. The introduction to the 4S study sums op evidence that is quite interesting, in light of the massive campaigns to reduce cholesterol that have by now gone on for years. Quote: "Expert panels in Europe and the USA have ... recommended dietary changes and, if necessary, addition of drugs to reduce high cholesterol concentrations – specifically LDL cholesterol – especially in patients with CHD. However these recommendations have been questioned, mainly because no clinical trial has convincingly shown that lowering of cholesterol prolongs life." Ref: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study. Lancet 1994;344:1383-9.

1994: A combined risk approach to prevention of heart disease is recommended by The *First Joint European Task Force of European and other Societies on Coronary Prevention*. Ref: Eur Heart J 1994;15:1300-31. These recommendations build on the Framingham risk equation.

1995: **The WOSCOPS study** (West of Scotland Coronary Prevention Study) documents the efficacy of primary prevention of CVD with a statin. This RCT shows that pravastatin significantly reduces the incidence of myocardial infarction and death from cardiovascular causes in men with relatively high cholesterol levels. Mortality in the treated group was 3,2%, as opposed to 4,1% in the placebo group. The intervention did not adversely affect death rates from other causes. The study was funded by Bristol-Myers Squibb who produces Pravacol (pravastatin). Ref: Shepherd J et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301-7.

1994-5: **"The fetal origin of adulthood disease hypothesis"** (also known as "The Forsdahl-Barker Hypothesis") becomes generally known in the medical community (See for instance Barker D. Fetal origins of coronary heart disease. BMJ 1995;311:171-4).
The roots of this hypothesis can be traced to Norwegian physician Anders Forsdahl's research on the population in Finnmark, Norway. He found that trends in the infant mortality and living conditions in childhood would predict cholesterol levels and mortality among men later (at age 40-69 years). He concluded that "The findings suggest that great poverty in childhood and adolescence followed by prosperity, is a risk factor for arteriosclerotic heart disease" (Forsdahl A. Br J Prev Soc Med 1977;31:91-5).
Barker stated that fetal under-nutrition in middle to late gestation, leading to a disproportionate fetal growth, "programmes" the organism biologically so that the risk of coronary heart disease in adult life increases. Since the Forsdahl-Barker hypothesis was launched, numerous studies have addressed the influence of weight patterns in childhood on subsequent CVD.

The 1990s: A series of **new statin drugs** enter the market. This gives rise to what has been called the "statin wars" in the highly competitive marketplace (the term appeared in the title of discussion papers in the Lancet in 2003-4).

1995: Primary angioplasty in the acute phase of cardiac events is introduced.

1996: The **CARDIA** study (see 1986) documents that experience of **racial discrimination increases blood pressure**. Ref: Krieger N. Sidney S. Racial discrimination and blood pressure: the Cardia Study of young black and white adults. Am J Publ Health 1996;86:1370-8.

Around 1996: Evidence is now accumulating that **the effect on statins** is not simply attributable to inhibition of cholesterol synthesis and thereby decreasing cholesterol levels, but also to **anti-inflammatory** effects that reduce development of atherosclerotic process in the vessel walls. See for instance "Statins do more than lower cholesterol", a Viewpoint paper by Vaughan C et al, Lancet 1996;348:1079-82.

1996: It is documented that plasma fibrinogen, a general marker of inflammation as well as of haemostasis, is determined by childhood conditions and adult psychosocial situation, i.e.: **negative life experiences appear to increase fibrinogen levels**. Brunner E et al. Childhood social circumstances and psychosocial and behavioural Ref: factors as determinants for plasma fibrinogen. Lancet 1996;347:1008-13.

1996: **Statins are now called "miracle drugs"** and their underuse is noted in a seminal paper: Robert WC. The underuse of miracle drugs: the statin drugs are to atherosclerosis what penicillin was to infectious disease. Ref: Am J Cardiol 1996;78:377-8.

1996: Prominent scientists speculate that due to technological advance, heart attacks may be "gone with the century." Brown MS, Goldstein JL. Heart attacks: gone with the century. Science 1996;272:629.

1998: **The UKPDS (UK Prospective Diabetes Study)** publications appear:
Effect of blood pressure control: The conclusion is that "tight" blood pressure control in patients with hypertension and type 2 diabetes achieves a clinically important reduction (RRR 24-47%) in the risk of deaths related to diabetes, complications related to diabetes, stroke, progression of diabetic retinopathy, heart failure and deterioration in visual acuity.
The tight intervention group aimed for BP <150/85 mmHg (the achieved group mean was 144/82), and the control group's aim was 180/105 (achieving a mean pressure of 154/87).
See: UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. BMJ 1998;317:703-13.
Effect of intensive blood glucose control: The investigators interpret the study in the following way: "Since intensive glucose control with metformin appears to decrease the risk of diabetes-related endpoints in overweight diabetic patients, and is associated with less weight gain and fewer hypoglycaemic attacks than are insulin and sulphonylureas, it may be the first-line pharmacological therapy of choice in these patients."
See: Effect of intensive blood-glucose control with metformin on complications in

overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group Lancet. 1998;352:854-65.

A couple of years later, a debate paper was published in the BMJ by McCormack and Greenhalgh, titled "Seeing what you want to see in randomised controlled trials: versions and perversions of UKPDS data" (BMJ 2000;320:1720-3). The authors state that "many authors, journal editors and the wider scientific community interpret the UKPDS study as providing evidence of the benefit of intensive glucose control", but the authors underline that this was not a direct finding of the study.

1998: **The second Framingham Heart Study Prediction Score Algorithm** is launched.

1998: **The Second Joint European Task Force of European and other Societies on Coronary Prevention** launches its guidelines (Eur Heart J 1998;19:1434-1503), still building on Framingham data.

1990s: It gradually becomes evident in various studies that Framingham risk score algorithms tend to overestimate risk in European contexts (see references in Paper V of this thesis).

1990s: The pharmaceutical companies become the most profitable industry in the USA.

1998: **The HOT (Hypertension Optimal Treatment) study** is published. HOT included nearly 19 000 patients from 26 countries, inclusion criteria were DBP 100-115mm Hg. The participants were assigned to three different BP treatment targets. No notable difference was seen in total mortality or CVD outcome rates between the groups. Still, the author's conclusion is that it is best to reduce BP to 140/85 or lower. The study was sponsored by ASTRA who used the results extensively in marketing campaigns.
Hansson L et al. Effect of intensive blood -pressure lowering and low-dose aspirin in patients with hypertension: principal results of the optimal hypertension treatment (HOT) trial. Lancet 1998;351:1755-62.

1999: **The WHO-ISH (International Society of Hypertension) issue new guidelines on hypertension** (J Hypertens 1999;17:151-83).
Definitions: hypertension > 140/90; "high normal BP": 130-39/85-90; normal BP: < 130/85; optimal BP: < 120/80. In Norway, a group of physicians published a critical review paper of the problems they saw related to these new recommendations: (Hetlevik I et al.: *Kliniske retningslinjer for hypertensjon* [Clinical guidelines for hypertension]. Tidsskr Nor Laegeforen 1999;119:3037-41.) Following the release of the WHO guidelines, 888 GPs and other medical professionals from 58 nations sign a letter (16 March 1999) to WHO general director Gro Harlem Brundtland expressing concerns related to the "goals of treatment" that young, middle aged and diabetics should have normal or optimal blood pressure. Brundtland answers (4 May 1999) that the guidelines had been developed by "eminent international experts using the latest information from epidemiological studies and randomised controlled trials." She also acknowledges that

the methodology for guideline development is under revision at the WHO.
(see http://www.uib.no/isf/letter/norsk.htm, http://www.uib.no/isf/letter/reply.htm).

1999: **Psychosocial factors and coronary heart disease:** a state of the art overview paper titled "Evidence based cardiology: Psychosocial factors in the aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies" is published by Hemingway H, Marmot M. BMJ 1999;318:1460-7. A psychosocial factor is defined as "a measurement that potentially relates psychological phenomena to the social environment and to pathophysiological changes." A key message is that: "Prospective cohort studies provide strong evidence that psychosocial factors, particularly depression and social support, are independent aetiological and prognostic factors for coronary heart disease."

1999: **"Atherosclerosis – an inflammatory disease"**, is the title of a seminal paper by Ross R. in N Engl J Med 1999;340:115-26. This paper draws attention to the novel concepts of endothelial dysfunction and "inflammatory risk factors" for CVD, such as C-reactive protein (CRP) and Interleukin -6 (IL-6). Quote: "the process of atherogenesis has been considered by many to consist largely of the accumulation of lipids within the artery wall, however it is much more than that. Despite changes in lifestyle and the use of new pharmacological approaches to lower plasma cholesterol concentrations, cardiovascular disease continues to be the principle cause of death in the USA, Europe and much of Asia. In fact, the lesions of atherosclerosis (…) can best be described as an inflammatory disease."

1999: A special communications paper is published in the JAMA, titled "Avoiding the unintended consequences of growth in medical care: how might more be worse?" The authors discuss potentials for harm related to increasing medical activity in various fields. In particular, they focus on the fact that "If individuals with cholesterol levels higher than 5.17 mmol/l are defined as abnormal, more than half the US adult (>17 years) population is labelled as diseased." Ref: Fisher ES, Welch HG. JAMA 1999;281:446-53.

2000: Primary results from the **ALLHAT** (Antihypertensive and Lipid-Lowering treatment to prevent Heart ATtack) trial, investigating major cardiovascular events in hypertensive patients randomized to doxazosin vs. the thiazide chlorthalidone. Investigators´ conclusion: Our data indicate that compared with doxazosin, chlorthalidone yields essentially equal risk of CHD death/nonfatal MI but significantly reduces the risk of combined CVD events, particularly congestive heart failure, in high-risk hypertensive patients. (JAMA. 2000;283:1967-75). The ALLHAT study came to influence guideline development and medical opinion strongly in the time period until 2005. For instance, the JAMA later printed an editorial stating that "The verdict from ALLHAT: thiazide diuretics are the preferred initial therapy for hypertension." Ref: JAMA. 2002;288:3039-42.

2001: The **statin cerivastatin (marketed in 1998) is withdrawn** from the US market due to a high reported risk of rhabdomyolysis (muscle destruction leading to renal failure). The JAMA published a paper on this topic in 2004, titled "Potential for conflict

of interest in the evaluation of suspected adverse drug reaction. Use of cerivastatin and risk of rhabdomyolysis" Ref: Psaty et al. JAMA 2004;292:2622-2631. Quote: "The history of cerivastatin illustrates a flaw in the current US system for SADR (serious adverse drug reactions) reporting and monitoring … the asymmetry between the information available to the company and the information available to physicians and patients seems striking …When serious, even rare SADRs such as rhabdomyolysis are detected, pharmaceutical companies have a complex and almost insurmountable conflict of interest in weighing and interpreting the risks and benefits of various courses of action. A subjective element is present in the effort to infer whether or not the occurrence of untoward outcomes in particular users of that drug was actually the consequence of that drug. For pharmaceutical companies, this appraisal may be influenced both by economic considerations and the emotional investment of those involved in the developing process." The authors conclude that "The US congress should mandate and provide adequate support for independent reviews and analysis of post marketing data."

2002: The PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) lipid study (Shepherd J et al. Lancet 2002;360:1623-30). Pravastatin did not reduce total myocardial infarction or stroke in the primary prevention group aged 70 years+, but it did so in the secondary prevention subgroup (ARR 4,3%, NNT 23 for 3,2 years). Total mortality was the same in pravastatin and placebo group, because an increase in cancer deaths outweighed the reduction in fatal CVD events.

2002: **The BMJ publishes a special issue on the topic of medicalisation**, titled: "Too much medicine?" on 13 April.

2002: The BMJ publishes a paper titled **"Risk factor thresholds: their existence under scrutiny"** (Law MR, Wald NJ. BMJ 2002;324:1570-6.). Key message: **The goal is not to "normalise" risk factors down to a given threshold, but to reduce them as much as possible in everyone**. This would mean treating everybody beyond a certain age (such as 55 years) as well as everyone with a history of CVD, irrespective of measured risk factor levels, instead of close monitoring of selected risk factors. Terms like "hypertension" and "hypercholesterolemia" should now be down-played. The same argument can be found in the paper "Hypertension – time to move on" by MacMahan S et al., Lancet 2005;365:1108-9.

2002: Publication of the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, indicating that the drug losartan, an angiotensin II receptor antagonist named Cozaar, appears to be more favourable than the beta blocker atenolol in preventing CVD events, both in patients with and without diabetes. Refs: Lancet 2002;359: pg 995-1003 and pg. 1004-10.

2002: The ALLHAT-LLT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) is published. In this trial, Pravastatin did not significantly reduce total myocardial infarction and total stroke (RR 0.91), nor total mortality (RR 0.99), as compared to "usual care" (the difference between the intervention group and usual care group involved lower thresholds for drug intervention, so that it tripled the num-

ber of patients receiving statins). The total number of serious adverse events is not reported in the paper. Ref: JAMA 2002;288:2998-3007.

2002: The MRC/BHF Heart Protection Study (HPS) of cholesterol lowering with simvastatin in 20.536 high-risk individuals: a randomised placebo-controlled trial is published in the Lancet (2002;360:7-22). Patients 40-80 years with coronary disease, other occlusive arterial disease, or diabetes who are treated with simvastatin experienced fewer coronary events than the placebo group, regardless of base-line LDL. All-cause mortality was also significantly reduced in this study.

2002: The Lancet publishes a Viewpoint paper by the first author of the WOSCOPS study (1995) **suggesting to abandon the "treat-to-target" strategy for cholesterol in favour of adopting a "fire and forget" approach**. The key message is similar to that of the previously mentioned BMJ paper; attempts to treat to ideal targets (Cholesterol < 5mmol/l or LDL < 3mmol/l) has no sound scientific basis and do not represent the best use of restricted resources. It is known that many (most) CVD events occur in patients with only modestly elevated disease risk, and that reducing cholesterol concentration to a moderate extent by use of small statin doses can be beneficial to many more people than those currently considered for therapy.
Ref: Shepherd J. Resource management in prevention of coronary heart disease: optimising prescription of lipid-lowering drugs. Lancet 2002;359:2271-3.

2003: Two review papers summarise the biomedical evidence base regarding statin use. The conflicting conclusions make it difficult for the non-expert to find out what is best to do:
1. "Statins can lower LDL cholesterol concentration by an average of 1.8 mmol/l which reduces the risk of IHD events by about 60% and stroke by 17%." Ref: Law MR et al., BMJ 2003;326:1423.
2. "The CV benefit has not been reflected in 2 measures of overall health impact, total mortality and total serious adverse events. Statins have not been shown to provide an overall health benefit in primary prevention trials." Ref: Therapeutics initative, University of British Columbia, April-May 2003, p. 48.

2002: An International Network of Cholesterol Sceptics (THINCS) is established, see their website at www.thincs.org. "THINCS is a steadily growing group of scientists, physicians, other academicians and science writers from various countries. Members of this group represent different views about the causation of atherosclerosis and cardiovascular disease, some of them are in conflict with others, but this is a normal part of science. What we all oppose is that animal fat and high cholesterol play a role. The aim with this website is to inform our colleagues and the public that this idea is not supported by scientific evidence; in fact, for many years a huge number of scientific studies have directly contradicted it." Medical doctor and researcher Uffe Ravnskov, a central member of THINCS, has authored the book "The Cholesterol Myths. Exposing the fallacy that saturated fat and cholesterol cause heart disease". Washington DC: New Trends Publishing, 2000.

2003: Publication of the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-

Lipid Lowering Arm) study which is stopped prematurely. This is the first study assessing the benefits of cholesterol lowering in the primary prevention of coronary heart disease (CHD) in hypertensive patients who are not conventionally deemed dyslipidaemic. 10.305 ASCOT participants with non-fasting total cholesterol concentrations 6.5 mmol/L or less were randomly assigned additional atorvastatin 10 mg or placebo. The investigators conclude: "The reductions in major cardiovascular events with atorvastatin are large, given the short follow-up time. These findings may have implications for future lipid-lowering guidelines." RRR for nonfatal MI and fatal CHD was 36%, ARR is 1,1% in 3 years. NNT to avoid one myocardial infarction is 313 patients for one year.

2003: A study documents that **social class in childhood appears to be associated with high diastolic and high systolic blood pressure in adult life**. The researchers reported stronger evidence of an increase in the effect of childhood social class with age, which seems to be largely accounted for by current body-mass index, which is strongly associated with blood pressure and might itself be affected by early life environment.
Hardy R et al. Birthweight, childhood social class, and change in adult blood pressure in the 1946 British birth cohort. Lancet 2003;362:1178-83.

2003: **BMJ publishes a special issue, titled: "Time to untangle doctors from drug companies"** on May 31st.

2003: **The European SCORE risk estimation system** is presented (see Papers IV and V in this thesis). It is based on data from 12 European cohort studies, including two from Norway. In total, more than 200 000 individuals are included in the base cohort, resulting in almost 3 million person-years of observation. The SCORE system addresses risk for fatal cardiovascular disease events.

2003: The Third Joint European Task Force of European and other Societies on Coronary Prevention issue **guidelines on CVD prevention in clinical practice on the basis of the SCORE system** (Eur Heart J 2003;24:987-1003.) Recommendations: Blood pressure should be < 140/80 (and lower in the presence of diabetes). Total cholesterol should be < 5mmol/l. See Papers IV and V in this thesis.

2003: **Various new hypertension guidelines are issued**. Common trend is now "the lower the better", treat above 140/90mmHg in everyone, and go lower in diabetes.
In particular, The US Joint National Committee (JNC 7) issues new guidelines: Hypertension is defined as > 140/90, and normal BP as < 120/80. The guidelines introduce the category pre-hypertension (BP 120-139/80-89) for which medical advice and surveillance is specifically indicated. The rationale behind this is that "Studies show that the risk of death from heart disease and stroke begins to rise at blood pressures as low as 115/75 mmHg, and that it doubles for each 20/10 mmHg increase."
See Ault A. Latest US hypertension guidelines create new "pre-hypertensive" category. Lancet 2003;361:1798.

2003: **The "Polypill" idea is launched in a BMJ theme issue** on June 28. The main research paper in this issue is: Wald NJ and Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419-23.

Concept: The Polypill would be designed so as to contain: three different blood pressure medications in low doses, a statin, aspirin (platelet inhibitor) and folic acid (according to the still controversial homocysteine theory of arteriosclerosis, insufficient dietary intake of the B vitamins, folic acid and pyridoxine leads to elevation of blood homocysteine which has been found to be associated with development of atherosclerosis.) The indications for the Polypill would be wide, but in particular, it would be appropriate primary prevention in any individual aged 55 years or older. In his column Editor's choice, BMJ Editor Richard Smith writes that BMJ readers should keep this particular issue as a collectors item, as "it is perhaps more than 50 years since we published something as important (…)." The Polypill papers immediately initiate a debate and lead to critique about the way results from individual drugs trials were combined and extrapolations made about their potential combined effects, in the absence of evidence from clinical trials.

In the 2004 BMJ Christmas issue, the concept "polymeal" is introduced with a touch of irony under a section called "Limits of medicine." The authors seriously state that the theoretical evidence that a polymeal[166] might reduce CVD by 75% in the population is theoretically equally strong as the research evidence in favour of the "polypill".
Ref: Franco OH et al. BMJ 2004;329:1147-50.

2004: **NICE** (National Institute of Clinical Excellence in England) **hypertension guidelines** are issued. Hypertension is defined as > 140/90, but treatment is recommended if BP > 160/90, or from 140/90 in the presence of increased CVD risk (as specified in the guidelines). The 'old' drugs thiazides and beta-blockers are advocated as first-line treatment in most patients.

2004: New **British Hypertension Society Guidelines (BHS-IV)** are published (see Williams B et al. BMJ 2004; 328:634-40). These guidelines aim to adapt the current therapeutic approach (as reflected in other guidelines) to the context of the National Health Service. In an accompanying BMJ editorial, it is stated that the prevalence of hypertension (>140/90) is 42% in the UK population aged 35-64 years, and that the condition is controlled only in 10% of the hypertensive population (quoting data from Wolf-Maier K et al. in JAMA 2003;289:2420-2 and Hypertension 2004;43:10-17). As opposed to the NICE recommendations (see above), these guidelines recommend ACE-inhibitors as first-line treatment for younger, non-black patients.
In the wake of the BHS-IV guidelines, several practicing clinicians wrote letters to the BMJ (BMJ 2004;329:569-70). Simple workload estimates were presented, and one doctor asked whether the guideline authors had considered the practical implications of the guidelines. Another doctor asked where the evidence for the treatment recommendations is, as he finds the BHS's interpretation of the results of the ALLHAT and ASCOT trials unacceptable. A third GP asked "whether the biomedical disease model of hypertension had been accepted by the general public", and a fourth asked how he should inform individual patients about potential benefits and harms, as the guidelines did not even provide basic information such as estimates of numbers needed to treat. He added "As a primary care doctor, I cannot know whether in any individual case I am doing more harm or good to my patient in diagnosing hypertension."

[166] The polymeal would include a regular intake of wine (150 ml/day), fish (114 g, four times a week), dark chocolate (100g/day), fruits and vegetables (400g/day), garlic (2,7 g/day), and almonds (68g/day).

In response to these letters, the BHS-IV guideline authors replied that "If "the real world of general practice" cannot meet the challenges of modern health care, so changes in the service delivery are needed." (BMJ 2004;329:570-1). After a brief comment on the data from the ALLHAT and ASCOT studies, they conclude that: "Service redesign, coupled with the effective implementation of current guidance, will continue to prove the nation's cardiovascular health."

The same BMJ issue where the letters criticising the BHS-IV guidelines appear, features an editorial titled "Treating hypertension with guidelines in general practice: Patients decide how low they go, not targets". (Campbell N, Murchie P. BMJ 2004;329:523-4). The editorial authors say that

> "Viewed from general practice, it seems that most articles on hypertension begin by reminding us of our failures. But is this justified? (…) for individual patients, the odds of benefit from small differences in target blood pressure or lipid concentrations are low. (…) To reach targets of 130-140, most patients will need up to four antihypertensive drugs (…) Current targets are low enough to be unachievable for most patients (…) For those who read them [the current guidelines] in detail, new levels of unwarranted complexity are to be found. Instead we rely on "user friendly" summaries emphasising (and failing to question) thresholds and targets without due reflection on the balance between what is desirable and what is achievable (…) Guidelines are based on average findings from selected populations and the opinions of experts on acceptable levels of risk. (…) Surprisingly, the patient's role in deciding his or her own blood pressure targets receives scant attention in guidelines for hypertension. (…) Appropriate management of blood pressure should therefore be guided by an informed dialogue between patients and doctors and not by blind pursuit of blood pressure targets."

2004: A Norwegian cardiologist and lead investigator of the LIFE, ASCOT and other hypertension studies, is being quoted in a major Norwegian commenting on the fact that doctors are being guided by Norwegian authorities to prescribe thiazides as the first-line drug to patients with uncomplicated hypertension (or specifically state the reason, if they choose another drug instead): "The authorities encourage us to take the patients lives with rat poison." Three medical doctors asked the Ethical committee of the Norwegian Medical Association to evaluate the interview. The story has later been covered in the News section of the BMJ: Mayor S. Doctors urged to present views in an objective way to the media. BMJ 2005;331 (Dec 3rd): 1289.

2004: **"Head to head" statin trials and "the new era of intensive statin therapy"**: These statin studies are no longer placebo controlled, but comparing high versus lower doses of statins, and different statins, in patients with established coronary heart disease: The REVERSAL trial concludes that among 654 randomised patients (502 evaluable by invasive ultrasound) patients with stable coronary heart disease: 80 mg atorvastatin is superior to 40 mg pravastatin in limiting progression of atheroma.
(Nissen SE et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. JAMA 2004;291:1071-80).
The PROVE-IT trial concludes that 80 mg of atervostatin is superior to 40 mg of

pravastatin in (rapidly) reducing cardiovascular events and total mortality.
(Cannon CP et al. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:350).
An editorial in the New England Journal of Medicine, accompanying the PROVE-IT study (Topol EJ. Intensive statin therapy – a sea of change in cardiovascular prevention, N Engl J Med 2004; 350:15), states: "Taken together, the REVERSAL and PROVE-IT trials herald a shake up of the field (…) a turning point -- that is the new era of intensive statin therapy." The author notes that statins account for the largest prescription drug expenditure in the USA at $12.45 billion dollars per year, but that only 11 of the 36 million US citizens who should be taking statins according to current guidelines are currently taking them.

2004: A 10 years follow-up of the 1994 4S study is published, documenting that the 5 year use of simvastatin in the original 4S study period was still associated with a survival benefit 10 years later. Ref: Strandberg TE et al. Lancet 2004;364:771-7.

2004: **Statins become available over the counter** (no prescription needed) in the United Kingdom.

2004: Attention is drawn to risk of fetal anomalies in presence of first trimester statin exposure. Ref: Edison RJ, Muenke M. N Engl J Med 2004; 350:1579-82.

2004: A large Austrian study on of sex-specific patterns in cholesterol levels on all-cause and cardiovascular mortality among 67413 men and 82237 women aged 20-95 years (15 years follow-up 1985-99) found that patterns of cholesterol levels showed marked differences between men and women in relation to age and cause of death. The role of high cholesterol in predicting death from coronary heart disease could be confirmed in men of all ages and in women under the age of 50. In men, across the entire age range, although of borderline significance under the age of 50, and in women from the age of 50 onward only, low cholesterol was significantly associated with all-cause mortality, showing significant associations with death through cancer, liver diseases, and mental diseases.
Ref: Ulmer H et al. Why Eve is not Adam: prospective follow-up in 149650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality. J Women's Health 2004;13:41-53.

2004: A US review paper titled "Drug treatment of hyperlipidemia in women" concludes that "For women without CVD, lipid lowering does not affect total or CHD mortality. Lipid lowering may reduce CHD events, but current evidence is insufficient to determine this conclusively." Ref: Walsh JME. JAMA 2004;291:2243-52.

2004: In UK, **a contract linking GP payment to quality of care** (as defined by 1050 attainable points linked to defined quality performance indicators, each point worth £120) is implemented. In this contract GPs with registered lists of patients (almost all citizens in the UK are registered with a GP) get financial reward for having monitored BT and cholesterol in patients with CVD during the previous 15 months, etc. Similarly, the higher the percentage of patients whose most recent BP was under 150/90 mmHg,

or cholesterol was under 5mmol/l, (both measured referring to the last 15 months), the higher the pay. Patients can be excluded from this calculation for specifically defined reasons, or if they do not attend an office visit despite three written reminders.
See for instance: Roland M. Linking physician's pay to the quality of care – A major experiment in the United Kingdom. N Engl J Med 2004;351:1448-54.

2004: **New US cholesterol recommendations are issued** on the basis of new information from the HPS, PROSPER, ALLHAT-LDL, ASCOT-LLA and PROVE-IT studies, recommending lower treatment goals for cholesterol: In individuals with high risk, LDL-C should be 2,6 mmol/l or lower, in moderate risk: 3,38 or lower; in low risk 4,16 or lower. Ref: Grundy SM et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004;110:227-239. In the wake of this, "The Cholesterol sceptics" send out a press release stating that "THINCS´ members are deeply disturbed by the ever-increasing pressure to lower blood cholesterol levels, and the underlying commercial interests that have distorted scientific research in this area. THINCS warns that statins have been excessively 'hyped' by the pharmaceutical industry and medical opinion leaders who have, unfortunately, become little more than paid advertorials."

2004: Medical journals agree to demand registration of all clinical trials, to be able to counteract publication bias (the fact that trials which show negative results of interventions trials have a tendency not to be published).
See: Clinical trials registration: A statement from the International Committee of Medical Journal Editors. Lancet 2004; 364: 911-12.

2004: **Estimations of the effect of unequal treatment on health in the US**:
Abstract: "The US health system spends far more on the "technology" of care (e.g., drugs, devices) than on achieving equity in its delivery. For 1991 to 2000, we contrasted the number of lives saved by medical advances with the number of deaths attributable to excess mortality among African Americans. Medical advances averted 176,633 deaths, but equalizing the mortality rates of Whites and African Americans would have averted 886,202 deaths. Achieving equity may do more for health than perfecting the technology of care." Ref: Woolf SH et al. Am J Epidemiol 2004;94:2078-81.

2004: **Various prominent editors and authors criticise what they believe to be undue medicalisation and marketing by 'Big Pharma'**
* John Abramson, family physician and teacher at Harvard Medical School publishes the book Overdo$ed America. The broken promise of American medicine. (See reference list).
* Marcia Angell, former editor-in-chief of the New England Journal of Medicine and senior lecturer at Harvard Medical School publishes The Truth About the Drug Companies: How They Deceive Us and What to Do About It (New York: Random House).
* Jerry Kassirer, another former editor-in-chief of the New England Journal of Medicine, argues that the industry has deflected the moral compasses of many physicians in the book On the take: how medicine's complicity with the big business can endanger your health. (New York: Oxford University Press).
* Richard Horton, current editor–in–chief of the Lancet writes: "Journals have devel-

oped into information laundering operations for the pharmaceutical industry." (Horton R. The Dawn of Mc Science. New York Rev Books 51(4):7-9).
2004: Richard Smith, at the time editor-in-chief of the BMJ gives a talk titled: "Medical journals are an extension of the marketing arm of pharmaceutical companies". In 2005, a paper based on this talk (with the above mentioned title) is published in PloS Med 2(5):e139 (open access via www.plosmedicine.org). Quote: "Journal editors are becoming increasingly aware of how they are being manipulated and are fighting back, but I must confess that it took me almost a quarter of a century editing for the BMJ to wake up to what was happening. (…) Editors may thus be peer reviewing one piece of a gigantic marketing jigsaw – and the piece they have is likely to be of high technical quality. (…) An editor may face a frighteningly stark conflict of interest: publish a trial that will bring US$ 100 000 of profit or meet the end-of-year budget by firing an editor. (…) Journals should stop publishing trials. Instead protocols and results should be made available on regulated web sites. (…) Instead of publishing trials, journals should concentrate on critically describing them."

2002-2006: **Several papers on social inequalities and health are published from the Whitehall II study.**
It is generally documented that differences in medical care are unlikely to contribute to social or ethnic differences in coronary heart disease in the Whitehall II cohort. (BMJ 200;329:318). Here are some direct quotes from conclusions in Medline abstracts of the studies:
– The results suggest that moderate inflammation and immune activation may be processes through which low socioeconomic status increases disease risk.
(Brain Behav Immun 2003;17:286-95).
– Given the important roles of interleukin-6 and fibrinogen in hypertensive pathophysiology, these results indicate that psychological stress could promote hypertension through stimulating these inflammatory proteins.
(J Hypertens 2005;23:1001-7).
– Social position and psychosocial factors are associated with coronary disease, but the underlying pathophysiologic mechanisms remain unclear. In a sample of 283 nonsmokers, it was found that social position was inversely associated with interleukin-6 and C-reactive protein and that participants with mild depression had impaired endothelial function (Am J Cardiol 2003;92:984-7).
– We have demonstrated an "economic difficulties gradient" in coronary events in men that is independent of other markers of socioeconomic position and appears to be only partially mediated by well-known risk factors in mid-life.
(Int J Epidemiol 2005;34:640-8.)
– Job control plays an important role in modulating cardiovascular and affective responses over the working day, and these responses may contribute to increased cardiovascular disease risk (J Hypertens 2004;22:915-20).
– [after adjusting for other factors] The level of justice at work remained an independent predictor of incident CHD. Conclusion: Justice at work may have benefits for heart disease (Arch Int Med 2005;165:2245-51).
– The results indicate that low control at home predicts CHD among women but not among men (Soc Sci Med 2004;58:1501-9).
– The experience of psychological distress confers increased risk of CHD in men that

is not explained by health behaviours, social isolation or work characteristics. The increased risk of CHD associated with psychological distress is not consistently demonstrated in women (Int J Epidemiol. 2002; Feb31(1):248-55).
– Lower socioeconomic status is associated with delayed recovery in cardiovascular function after mental stress. Impaired recovery may reflect heightened allostatic load, and constitute a mechanism through which low socioeconomic status enhances cardiovascular disease risk (Eur Heart J 2002 Nov;23(22):1757-63).
– Stress at work is an important risk factor for metabolic syndrome. The study provides evidence for the biological plausibility of the link between psychosocial stressors from everyday life and heart disease (Chandola T et al. Chronic stress at work and the metabolic syndrome: prospective study. BMJ 2006; Feb 14; [Epub ahead of print].)

2004: **The Canadian-coordinated INTERHEART study**, including more than 29.000 people in 52 countries and from all inhabited continents of the world, found that the two most important risk factors are cigarette smoking and an abnormal ratio of blood lipids (Apolipoprotein B/Apolipoprotein A-1), which together predicted two-thirds of the global risk of heart attack. Additional risk factors are high blood pressure, diabetes, abdominal obesity, stress, a lack of daily consumption of fruits and vegetables and a lack of daily exercise. Regular consumption of small amounts of alcohol was found to be modestly protective. Worldwide, these nine factors collectively predict more than 90 per cent of the risk of a heart attack. The president of the Canadian Institutes of Health Research, said that "This is a landmark study. It suggests that a combination of lifestyle changes including stopping smoking, eating a healthier diet and exercising could lead to an 80 per cent reduction in the risk of heart attacks … The INTERHEART study provides the health research evidence needed to build national and international programs for the prevention and control of one of the leading cause of death in Canada and world-wide." Ref: Yusuf S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937-52.
Another INTERHEART publication goes deeper into the theory that psychosocial stressors are associated with increased risk for myocardial infarction. Odds ratio for MI in the presence of "permanent general stress at work or home" is found to be 2.17 (CI 1.84-2.55), as compared to absence of general stress. (Rosengren A et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11.119 cases and 13.648 controls from 52 countries (the INTERHEART study): case control study. Lancet 2004;364:953-62.)

2004: The US **ACE study** documents that **Adverse childhood events increases the risk for CVD**. A retrospective US study involving approx. 17 000 participants documents that adverse childhood experiences, including abuse, neglect, and household dysfunction, were significantly associated to development of ischemic heart disease in a clear dose-response fashion, with an Odds ratio of 3,6 (95%CI 2.4-5.3) for ischemic heart disease among persons with the highest ACE score (Dong M et al. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation 2004;110:1761-6.). The ACE study has been described in the theoretical introduction to this thesis. See the ACE study page on the CDC homepage: (http://www.cdc.gov/nccdphp/ace/index.htm).

2004: A Danish diabetes researcher protests against new recommendations for intense multi-pharmacological treatment in diabetes, He believes that "We must make an effort to draw more differentiated conclusions from these [UKPDS, 4S] and similar research results". "If a patient with type 2 diabetes is to have 2 anti-diabetic preparations, 3 antihypertensive drugs, a lipid-lowering agent and treatment for co-existing chronic disease, no one can foresee the consequences in the form of side effects and interactions, not to mention the fact that patients do not always take their medications as prescribed." Ref: Olivarius N. Diabetes care today: not everyone should have intensive multipharmacological treatment. Scand J Prim health Care 2004;22:67-70.

Sept 2004: Former US president **Bill Clinton has a completely unexpected "heart scare"**, and undergoes quadruple bypass surgery only a few days after his disease is recognised. Since Bill Clinton had generally been considered very fit, this event had widespread effects in the US healthcare system and also posed many tricky questions to the medical community and population in general:

- Is the following good advice: "If people have a family history there, and high cholesterol and high blood pressure," Clinton said [in an interview with Larry King], "they ought to consider the angiogram." (Gupta S. Clinton's big test. TIME Sept 20 2004;164:77).
- Professionals and lay people all wondered: "When I read that President Clinton learned for the first time in early September that he had severe heart disease, I was shocked. His health must have been monitored as closely as anyone's. How could something this serious have escaped his doctors' notice? An how can someone who looked so healthy and vigorous as he did in July (...) actually be living with an unrecognized disease that could take his life at any moment?" (Harv Health Lett 2004;30:8).
- "In the days following Bill Clinton's quadruple bypass last Monday, Dr. Harvey S. Hecht, the director of preventive cardiology at Beth Israel Medical Center in New York, received twice as many calls as usual from concerned middle-aged people, largely men. Most of the callers were worried that they might be *just like Mr. Clinton -- seemingly healthy, cardiological time bombs*". ("Yipes, Clinton! That Could Be Me." New York Times Sept 12th 2004).
- Even the best informed and powerful people make surprising health choices: According to The American Journal of Managed Care, Clinton chose to have his surgery at a hospital with a published mortality rate that was twice the average for the State of New York. The author wonders "How can one of the smartest presidents, a technocrat, and a healthcare policy wonk ignore this information and place his life in the hand of a "statistical outlier"? He then comes to the conclusion that "The right decision then involves more than a hospital and physician ranking." (McMahon LF. Am J of Managed Care 2004;Oct:664).

2005: The infectious disease aetiology for heart disease (TWAR hypothesis, see year 1988) is deemed unlikely as a cause of heart disease in a review paper.
Ref: Danesh J. Antibiotics in the prevention of heart attacks. Lancet 2005; 365:365-6.

2005: A US review paper on safety of statins concludes that currently available statins are generally safe, given correct prescription, attention to conditions that predispose for development of severe myopathy, and attention to drug interactions. It is noted that

side effects tend to be dose related, and that this is important to bear in mind now that current recommendations go in direction of "the lower, the better", requiring increasing statin doses. Six statins are currently available by prescription in the US.
Ref: Grundy SM. The issue of statin safety. Where do we stand? Circulation 2005;111:3016-9.

2005: The world's most best-selling drug is Atorvastatin (Lipitor), the sales account for half of the manufacturer Pfizer's annual profits. In a paper titled "Torcetrapib and Atorvastatin, should marketing drive the research agenda?" a Harvard professor expresses deep concerns about Pfizer's research on a new type of cholesterol drug (torcetrapib – designed to increase HDL). In the on-going clinical trials, the new drug is linked to Lipitor in such a way that "current trial design may not optimally meet scientific needs of prescribers, the clinical needs of patients, the economical need of payers, or the regulatory need of policymakers. But they superbly meet the business needs of the sponsor – to create new knowledge in a way that will protect market share of the largest company's most important product. The author calls for research that is independent of industrial sponsors (Avorn J. N Eng J Med 2005;352:2573-6).

2005: Revisiting the **"fetal origins of adulthood disease hypothesis"** (Forsdahl-Barker hypothesis, see entry at 1994-5). A BMJ editorial summing up recent evidence says: "Although the evidence for an association between impaired fetal growth and increased risk of coronary heart disease is compelling, it is premature to make policy recommendations in order to increase birth weight. (…) In the future, individual tailoring of life-style and pharmacological interventions according to early growth patterns and genetic setting may maximise benefits in the prevention of cardiovascular disease." "Attending to the health of women of reproductive age will have a profound impact on the wellbeing of their offspring. The importance of this issue closely parallels WHO's *World Health Report 2005* – making every mother and child count" (Eriksson JG. The fetal origins hypothesis – 10 years on. BMJ 2005;330:1096-7).
The fetal origin hypothesis has generally focused on effects of maternal under/malnutrition as well as placental insufficiency. It remains to be investigated whether low-weight births that are attributable to psychosocial stress such as racism can have a similar programming effect on the predisposition for cardiovascular (or other) disease in the offspring as under-nutrition. The CARDIA study has shown that women who are exposed to racism have an increased risk of premature and low-birthweight deliveries (Mustillo S. Am J Publ Health 2004;94:2125-31). A study in rats showed that maternal exposure to stress altered the cardiovascular response pattern to stress in the adult offspring in a direction which is associated with CVD in humans (Igosheva N et al. J Physiol 2004;557.1:273-285.)

2005-6: **Various findings relate life experience to risk for CVD:**
– It is documented that high levels of phobic anxiety are associated with an increased risk of fatal coronary heart disease, particularly from sudden cardiac death. Some, but not all of this risk can be accounted for by CHD risk factors associated with phobic anxiety. (Albert CM. Circulation. 2005 Feb 1;111(4):480-7.). This association has previously been demonstrated, but only among men.
– Publications in Circulation on a the link between depression and inflammatory markers:

Empana et al. Circulation 2005;111:2299-2305: "These data support an association between depressive mood with inflammatory markers and suggests that depressive mood is related to coronary heart disease even after adjustment for these inflammatory markers."
In an editorial titled "Depression and cardiovascular disease. A call for recognition," two cardiologists state that the association between depression and CVD appears to be strong, but that the nature of the relationship is still unclear; i.e. to what degree depression is a causal risk factor, an associated risk marker, or a secondary event. It is also unclear to what extent medical treatment of depression influences prognosis. The evidence however indicates that depression does play a significant aetiological role. The authors are concerned about the issue being mainly ignored in mainstream cardiology:

> "Depression, however, remains largely off the radar screen of cardiac care (…) Unfortunately the intense focus on mechanistic relationships appears to be distracting from a clinical patient-focused reality (…) Because co-morbid conditions strongly influence treatment plans and prognosis, it makes no sense to treat cardiovascular disease in a silo" (Rumsfeld JS, Ho M. Circulation 2005;111:250-253).

– A Finnish study on organisational injustice and impaired cardiovascular regulation among female employees concludes that "The findings are consistent with the hypothesis that cardiac dysregulation is one stress mechanism through which low perceived justice of decision making procedures and interpersonal treatment increases the risk of health problems in personnel" (Ref: Elovainio et al. Occup Environmental Med 2006; 63:141-4.)

2005: Publication of **the ASCOT-BPLA study** (the antihypertensive arm of the Anglo-Scandinavian Cardiac Outcomes study). This is the largest randomised antihypertensive trial ever conducted in Europe, involving almost 20 000 patients with hypertension and at high risk for CVD. Patients were allocated to one of two treatment regimens (i.e. not single drug classes, as in most preceding trials) testing the primary hypothesis that "a newer antihypertensive treatment regimen (calcium channel blocker+/- an ACE inhibitor is more effective than the older regimen (beta-blocker +/- a diuretic) in primary prevention of coronary heart disease." The trial was stopped prematurely, when the Data and safety monitoring board reported that patients on the atenolol-based regimen were being increasingly disadvantaged. In terms of primary heart disease endpoint reduction, the trial did not demonstrate statistically significant results, but on the basis of secondary endpoint reduction, the investigators conclude that "The amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen" and that (...) "the results have implications with respect to optimum combinations of antihypertensive agents" (Lancet 2005;366:869-71 and 907-13).
When the ASCOT study was published, it created what several commentators call a "media hype"; i.e. it received promotional publicity of an extravagant and even contrived kind.

2005: Debate over the ASCOT-BPLA trial
As the only entry on this time-list regarding debates on drug regimens, I will highlight the debate which followed the ASCOT study trial, since it raises several questions that

are both interesting and typical in the wake of publication of major drug intervention studies where major financial interests are involved.
This can be well exemplified by an editorial in the BMJ (McDougall C et al. BMJ 2005;331:873-60). It is written by three authors, of whom two state competing financial interests, and has the title "ASCOT: a tale of two treatment regimens." The editorial states that "The trial compared strategies combining more expensive newer drugs with cheaper older ones." The editorial states that patients in the "new drug regimen" fared significantly better regarding secondary endpoints. These patients also developed fewer new cases of diabetes type 2. So guidelines on hypertension such as those from NICE should now be rewritten.
Several letters to the BMJ Editor disagree with the conclusions of the editorial (the letters can be accessed through the BMJ website). Some examples of arguments:

- A GP (member of the association "No-free-lunch") writes: "Newer is always better. This editorial uses the word "newer" no less than 7 times as it seeks to usher a new era in the politics of hypertension. Oddly enough these "newer" medications are some 20 years old so the choice of such provocative language is interesting (...) In ASCOT, even if we assume that the observed difference between the treatment arms is not merely related to a simple lowering of blood pressure of 2.1 mmHg – which is a big IF - the NNT per year to prevent death would be around 645 and for any vascular event 220. Diabetes is an arbitrary point on a metabolic continuum and therefore any reduction in incidence is questionable especially with annual NNT of over 200."
- A prescribing team manager writes that "We shouldn't lose our heads over ASCOT": "ASCOT merely adds to our understanding of the importance of managing blood pressure effectively. It does not cancel out the key trials of the past. In the same way ALLHAT gives an indication of the benefit of diuretics in treating hypertension. ASCOT does not trump ALLHAT and the authors' assertion that diuretics will become adjunctive treatment is not supported by the evidence. The difficulty we have with ASCOT is interpreting the absolute value of the results given that the trial itself was stopped before the primary end-point reached clinical significance. Had the trial been allowed to continue would it have shown a clinically significant difference in the primary end-point? We do not know. We should not overlook the importance of some of the secondary endpoints but equally we need to see them in context, and appreciate the absolute risk reductions (ARR) and numbers needed to treat (NNT) rather than the relative risk reductions (RRR) that the editorial misleadingly quotes:
  All cause mortality: ARR = 0.87%; RRR = 11%; NNT = 115¸ Cardiovascular mortality: ARR = 0.83%; RRR = 30%; NNT = 120; Coronary events: ARR = 1.04% RRR = 13%; NNT = 96; Stroke: ARR = 1.00%; RRR = 29%; NNT = 100.
- An expert in prescribing and clinical effectiveness indicates something that Richard Smith expressed concern about in 2004 (see above); the fact that treatment doses may be purposefully selected so as to disfavour the "old" one: "I am puzzled why, given the evidence base, that a thiazide was not chosen as the first-line drug in the 'old arm' and when atenolol was chosen, why the dose was increased to 100 mg daily. The BNF has, for as long as I can remember, advised not to go above 50mg daily as all you do is increase side-effects. How much

has this 'high' dose of atenolol contributed to new -onset diabetes? It is not surprising therefore that the 'old arm' lowered BP less effectively. What happened to the third line drug, doxazosin? Was it used more frequently in the atenolol arm? Given its poor performance vs. thiazide in ALLHAT, this might be very important information. For an alternative view of ASCOT-BPLA, and in my opinion a more reasonable one, I would direct readers to http://www.pharmj.com/pdf/spectrum/pj_20051001_ascot.pdf".

– A GP writes: "For the first time I find myself slightly uneasy about what degree of competing interests we are supposed to consider among the authors of this editorial. It surely makes a difference whether the authors have received a few hundred pounds for sacrificing an evening to give a talk sponsored by a drug company, or, alternatively, whether the amount over a one or two year period is a hundred thousand pounds. The former would not affect my opinion as to the independence of their views. The latter amount would. It is certainly helpful to know that the authors have competing interests, but to be truly useful to readers I think it is necessary to quantify the size of those competing interests. It is not unreasonable to expect transparency in those putting themselves forward as opinion formers for the profession."

2005: "The trial was stopped early for benefit." A systematic review in the JAMA reports that this is becoming an ever more common scenario in the world of medical research: Investigators announce in a major medical journal that the drug they've been testing has proven so effective that they've stopped the trial, to provide the drug's benefit to all patients involved. The anchoring author of the JAMA paper is Gordon Guyatt, one of the pioneers of EBM. The study analysed 143 RCTs that had been stopped early for benefit, of which 92 had been published in 5 high-impact medical journals. The conclusion is that it is becoming ever more common *to stop major randomised controlled trials early "for benefit"*, with *"clustering of publication in the top general medical journals"*. The authors note that such truncated trials "often receive considerable attention", but that the information underlying the decision to stop may be quite poorly reported. "We noted limited reporting of critical features specific to the decision to stop the trial." The results of truncation however go in direction of "implausibly large treatment effects, particularly when the number of events is small. These findings suggest that clinicians should view the results of such trials with scepticism."
Ref: Montori VM et al. Randomised trials stopped early for benefit. A systematic review. JAMA 2005; 294:2203-9.
In an interview with Health Day, Guyatt describes the finding as "a real wake –up call." "While pharmaceutical companies may be sincere in their belief that patients benefit from stopping the trial early, it also improves the likelihood of marketing your drug" (www.healthday.com, Nov 1st 2005).

2005: **Scientific fraud – diet and CVD**: On July 30, the BMJ published a series of papers presenting a strong suspicion that the seminal 1992 BMJ paper on the cardioprotective effect of an Indio-Mediterranean diet (Singh RB et al, see year 1991) is based on scientific fraud; either data fabrication or falsification. The BMJ states that the 1992 paper rapidly became an influential "citation classic", frequently sited in other papers and clinical guidelines. In the same week (July 2005), editor Richard

Horton of the Lancet presents a similar concern related to Singh's 2002 Lancet paper on the effectiveness of diet. The 2002 paper on the beneficial effects of diet is included in the evidence base of the 2003 European guidelines on CVD prevention (reference 64 in the full version of the guidelines).

2005: A UK modelling study titled "How many antihypertensives do patients need to achieve target blood pressure" indicates that 54% of hypertensive men aged 35-74 years and 50% of women will require two to three drugs to reach the target of 140/90. 23% of men and 35% of women will require four drugs or more. Some patients will require as many as seven. (Marshall T. Journal of Human Hypertension 2005;19:317-9).

2005: **More on the homocysteine hypothesis of CVD: Intervention does more harm than good**

Observational studies have by this time consistently shown that higher plasma homocysteine concentrations are associated with a greater risk of CVD. However, the causal relationship between homocysteine and CVD is still unclear. Supplements of vitamin B (which is a complex that includes folic acid) have been shown to reduce plasma homocysteine. According to a classical pathophysiological rationale, vitamin B supplements should thereby decrease cardiovascular risk. (As previously noted, folic acid is one of the ingredients in the suggested "Polypill"). A new meta-analysis of 25 trials is then published, showing that daily doses of 0,8 g or more of folic acid are needed to achieve maximal reduction of homocysteine, 0,2g produce 60% and 0,4% 90% of the effect. (Am J Clin Nutr 2005;82:806-12). Then, a meta-analysis is published in the BMJ which questions the whole rationale for the homocysteine hypothesis in Western countries, and predicts that it is doubtful that folic acid will prevent CVD (BMJ 2005;331:1053-6).

Around the same time, the Norwegian intervention trial NORVIT study which investigated whether vitamin B supplementation prevents recurrent CVD among more than 4700 heart attack survivors, is presented. In addition to their standard heart medicines, the groups received either daily folic acid (itself a B vitamin), daily vitamin B6, both folic acid and vitamin B6 or placebo for three years. The results indicate that no subgroups of patients in the NORVIT trial benefited from taking B vitamins. After three and a half years, those who had been taking either folic acid or vitamin B6 alone had a small increase in the risk of cardiovascular disease (heart attack or stroke), compared with those who had received the placebo. However, those who had taken both folic acid and vitamin B6 each day had a 20% increased risk of heart attack and stroke, despite their homocysteine levels going down by up to 30%. The results also showed there was a 40% increase in the risk of new cancers in the group taking folic acid, which the researchers said warranted further investigation. Author Professor Kaare Harald Bønaa said: "The results of the NORVIT trial are important because they tell doctors that prescribing high doses of B vitamins will not prevent heart disease or stroke. "B vitamins should be prescribed only to patients who have B vitamin deficiency." (Source: BBC health news Sept 6th 2005; http://news.bbc.co.uk/1/hi/health/4218186.stm).

Since vitamin B has recently been promoted for heart patients, and many doctors have begun to treat their patients with vitamin B, the NORVIT results aroused much astonishment and got wide media coverage. A heart specialist however thinks that "Mass

media have reported and interpreted the preliminary results from NORVIT in a naive and unbalanced manner and concluded with a general statement that B-vitamins were generally harmful. This has resulted in considerable confusion, anxiety, scepticism not only in the general population, but also among doctors". (Schneede J. Preliminary conclusions from the NORVIT study, see www.rondellen.net/evaluation_eng.htm).
One month later, the smaller-scaled WENBIT (Western Norway B-vitamin Intervention Trial) is stopped, due to the scare created by the presentation of the NORVIT study.

END

Dissertations at the Faculty of Medicine, NTNU

1977

1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED IN VITRO

1978

3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979

5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980

6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS IN VITRO

1983

9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984

11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AN STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985

18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.

21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986

24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987

27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988

30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.
33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.
34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.

47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-□ AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.

71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
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77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: erbB ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.

98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE nuc GENE IN THE DIAGNOSIS OF Staphylococcus aureus INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
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109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION in mice infected with MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.

123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

1997

124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED IN UTERO.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR TNF AND LPS: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.

142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.

163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES

186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, COMORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

2002

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP

B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.

205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES

223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

2004

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY

243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

2005

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT

262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES

ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION

279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS

280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY