Summary

This study develops a **theory of drug discovery**. The thesis will be elaborated that medical-pharmaceutical practice is an indispensable source of feedback to the drug discovery process. As will be shown, the origin of new medicines lies in the interface of development in the laboratory and the application of therapy in daily medical practice. The various methods of gathering knowledge about pharmacotherapy, and the mechanisms through which practice contributes to the creation of new drugs will be clarified.

In elaborating this thesis, a model is developed in order to describe the drug discovery process. The starting point is the view that the development of medicines can be conceived of as a process of rapprochement between knowledge patterns on the one hand of drugs and on the other of diseases. The concept of profile that forms a central part of communicating knowledge in the pharmaceutical sciences and medicine is taken as the basis of the presented model. The epistemological view is developed that therapeutic development can be regarded as the movement of patterns between profiles of drugs and diseases. Subsequently, this view is transformed into a set-theoretical model of the drug discovery process.

The historical part of this study describes the evolution of the beta blockers and the calcium antagonists. Emphasis is on developments in the field of angina pectoris roughly covering the period 1950-1975. Various industrial projects were examined against the background of views on angina pectoris, heart failure and other cardiovascular diseases. The basic approach consists of the comparative analysis of developments in the Anglo-American and German speaking medical world with the emphasis on British and American medicine on the one hand and German medicine on the other. The differences described help to unravel processes relevant to therapeutic progress. The methods used are interviews with participants, literature-analysis and the assessment of citation patterns.

**Chapter 1** starts from the conflict between the controlled clinical trial and casual experience. The way through which the clinical trial has expelled casual experience as a true source of knowledge, and has structured drug research, will be discussed. The common view underlying the clinical trial misrepresents the role of clinical medicine in two respects. Firstly, it gives clinical medicine a place somewhere in the middle of a linear sequence of events, with general practice as the final station. Secondly, it narrows down the available clinical methods for gathering information ranking these and putting the controlled clinical trial at the top of the list. This might be correct when evaluation of knowledge is at stake, but this is certainly not the case from the viewpoint of the generation of medical knowledge.

In **chapter 2** the theoretical framework of the study is developed. In part 1 two sets of philosophical terms used in drug research, e.g. the distinctions “basic-applied” and “rational-empirical” will be discussed; with respect to the term “empirical” the terms of serendipity and art will also be examined. In part 2 the concept of profile is analysed while in part 3 a set-theoretical definition of this concept and a set-theoretical model of drug discovery are presented.

In **chapter 3** the early history of the beta blockers will be sketched in order to illustrate the way experimental and clinical characteristics of (new) drugs are clarified; this also forms the background for the historical developments in the subsequent chapters.
In chapter 4 some industrial projects in the beta blocker field are described. The projects at Imperial Chemical Industries (ICI) in the United Kingdom and AB Hässle in Sweden are examined in detail because both were at the frontiers of bio-medicine. The ICI team created famous drugs such as pronethalol, propranolol, practolol and atenolol, each of them starting a new episode in the beta blocker field. Because of the emphasis on angina pectoris, the development of atenolol in the context of antihypertensive therapy has been excluded. The Hässle team is described because of its different background compared with ICI, the close cooperation with academic and clinical scientists, the creation of important concepts in the field, and the development of important drugs, i.e. alprenolol and metoprolol.

In chapter 5 the curious history of verapamil is described. Developed as a coronary vasodilator for anti-anginal treatment, the drug was recognized as a beta blocking compound but after heated debate rejected as such. Being a dying drug in the treatment of angina pectoris, its resurrection was impressive when a novel type of action was unraveled. The elucidation of verapamil as a calcium antagonist has been acknowledged as the result of experimental work of Fleckenstein. For this reason the way Fleckenstein and co-workers disentangled the mechanism of action of verapamil will be described. Subsequently a scientometric analysis is performed to investigate how the concept of calcium antagonism has been accepted by the medical community. The “logic” of drug and disease profiles will be applied to highlight some events in the history of verapamil.

Chapter 6 discusses the development of Anglo-American views about angina pectoris. Though it covers roughly the period 1950 - 1980, emphasis is on major shifts occurring in late 1950s and early 1970s. It describes how the syndrome of angina of effort became a dominant category in clinical taxonomy of angina pectoris, and how it subsequently declined, creating room for new concepts. In this way the conclusion of the preceding chapter, i.e. that changes in views of angina pectoris were relevant to verapamil’s revival, will be elaborated.

Chapter 7 concerns the development of the beta blocker project at Boehringer Ingelheim in Germany. The Boehringer team possessed promising compounds at an early stage but was not able to achieve a dominant position in the field. From this viewpoint the project might be considered a failure. It is a privilege to be permitted to describe this project because access to inside material on failed projects in pharmaceutical-industrial research is seldom granted. However, failure delivers a mirror for the discontinuity and irregularity of scientific research. Putting the project in the context of German medicine it is shown that research at Boehringer was victim of medical views which appeared to be infertile soil for the development of the beta blockers.

In part 1 of chapter 7 the German medical views on coronary vasodilators in anti-anginal therapy, heart failure and angina pectoris are discussed. With respect to the views of coronary vasodilators and heart failure the views are contrasted with Anglo-American concepts. Regarding the German views of angina pectoris, the contrast with views in the British and American medical world described in chapter 6, becomes clear.

Chapter 8 discusses three issues. Firstly, the search process for drugs will be reconsidered in the light of the insights achieved and will be related to current concepts about rational drug design and screening. Secondly, two points of criticism relating to the model will be raised, i.e. the epistemological status of the concept of profile; and the issue to what extent
knowledge is explicable. Thirdly, the way medical-pharmaceutical practice contributes to
drug discovery will be systematically analyzed.
In chapter 9 the role of practice will be reconsidered in the context of the increasing
attention towards the study of bio-molecular processes. In criticizing this increasingly
popular view, the basic claim of this thesis, i.e. that the exchange of information between
biological sciences and medical-pharmaceutical practice is crucial to the discovery process,
will be elaborated anew.