

## Summary

The objectives of this thesis and the historical background of medical sciences in the time of Alexander Willem Michiel van Hasselt are presented in **Chapter I**. The historical definitions of 'beneficial' and 'adverse' venoms are given and the understanding of physiology, pharmacology in the 19th century is explained. Toxicology was an undivided, distinct discipline at the time Van Hasselt lived and worked. The empirical knowledge about venoms was adjusted by experimental work involving various animal species. Reports about these animal experiments had no defined section within the scientific literature and the effects of venoms in healthy animals were described in handbooks on pharmacology and toxicology and in books dealing with the *materia medica* in chapters about physiology, respectively. The observed physiological changes suggested the potential therapeutic effects and these were interpreted according to the actual diverse classification systems.

**Chapter II** provides a brief historical overview over the theories in toxicology until the beginning of the 20th century (World War I). Ancient Greek scientists described venoms as **φάρμακα** (Latin: *pharmaca*) and they were aware of the fact that venoms could be lethal but also beneficial in the treatment of diseases. Diseases as such were considered to be intoxications, and thus the 'toxon', the causative agent needed to be eliminated to restore the blocked organ functions. The most appropriate method to treat a patient was to apply a venom at increasing dosages until obvious signs of toxicity occurred. These therapeutic approaches were directed to regain the balance within the organism, by at the same time providing increasing information about the therapeutically effective versus the lethal dosages. By the end of the 18th century the use of venoms as therapeutic agents gained more and more criticism. Experimental work in animals was stimulated to increase the knowledge and to discriminate between desirable and non-desirable effects. The existing empirical knowledge was accomplished by these experimental results. In addition, chemical analytical methods became available and gained increasing influence in the discipline of toxicology. As a consequence, animal experiments could be conducted for the first time with isolated, pure substances, allowing distinct dynamic and kinetic studies. In this new scientific approach, initially French scientists played the leading role, followed by their German colleagues. Physicians in the Netherlands observed these new developments from a distance.

**Chapter III** describes the development of the discipline toxicology in the Netherlands. In the 18th century, the most prominent compound in the Dutch scientific literature was lead. Lead intoxications were not only observed following occupational exposure, but also following consumption of lead contaminated drinking water, wine and beverages in normal citizens. In addition, lead intoxication could occur as a consequence of the therapeutic use of lead derivatives. Physicians and pharmacists studied and described the array of clinical symptoms following lead exposure, whilst chemists tried to invent analytical methods to determine the lead concentrations.

**Chapter IV** is devoted to Van Hasselt and his family and intends to follow his career in the military medical services as well as in the scientific community.

**Chapter V** is devoted to the contributions of Van Hasselt to medical sciences. Three specific items, the gastric pump, the tobacco smoke clysmas, and the artificial respiration are described by Van Hasselt in detail according to the state of the art at his time and replenished with own experimental results. The gastric pump was at that time not in use in the Netherlands, but Van Hasselt considered this instrument to be essential in the therapy of patients with alcohol intoxication. The application of tobacco smoke via a clysmas resembled the empirical knowledge of the vitalistic epoch and the new approaches towards the restitution of respiration and blood circulation were based on physiologic experiments. The artificial respiration was considered to be an alternative for the tobacco smoke clysmas. Van Hasselt did not differentiate between new and old methods in patients in the state of suspended animation. The reconstitution of respiration had the highest priority, the method to achieve this, was of lesser importance. Van Hasselt developed a new method to assist respiration, which can be found even in the 20th century in the Dutch Red Cross brochures.

In 1856 the first issue of a book of Van Hasselt was published, entitled: "Handleiding tot de leer van het militair geneeskundig onderzoek, het visiteren der manschappen bij hunne intrede in en hunne verwijdering uit de dienst in verband met de ziekten en gebreken die voorgewend, nagebootst, willekeurig voorgebragt of voorbedachtelijk verborgen kunnen worden". This book describes the methods to identify malingerers and sham patients, wanting to escape military service or criminals, trying to avoid dismissing, respectively, due to various reasons.

**Chapter VI** is devoted to the activities of Van Hasselt in the development of the discipline toxicology. In his publications, Van Hasselt cited predominantly the findings of the international literature. In the middle of the 19th century the lecturers of the Military Training Hospital ('s Rijks Kweekschool voor Militaire Geneeskundigen, RKMg) were invited to provide syllabi for the different subjects they were teaching. Van Hasselt was one of the first to fulfill these demands, and published his "Handleiding der Vergiftleer" (System of instructions on the effects of venoms). As early as 1848 Van Hasselt has published a comprehensive handbook, entitled "De noodzakelijkheid van algemeen toezigt op het gebruik van vergiften" (The necessity to regulate the use of venoms), which was based on lectures presented for the Natuurkundig Gezelschap te Utrecht (a scientific association). In this book, Van Hasselt uses a classification system for intoxication, which was unique in his time. He allocates the known toxic substances to the following categories:

- intoxication, caused by lack of knowledge, recklessness, sweet tooth or ignorance,

- intoxication, caused by covetousness and shortcomings
- intoxication, caused by lay people (non-physicians)
- intoxication, caused by trades, occupations and factories
- intoxication, cause by intentional self-intoxication
- intoxication, intended for murder.

In his handbook, however, he uses the traditional classification systems which is based on the major sources of venoms: minerals, plants and animals.

The properties of all venoms were described very systematically by Van Hasselt, addressing for each compound the physico-chemical properties, the symptoms in case of acute and chronic intoxication, as well as possibilities for a treatment. Other books published in his time, just addressed the signs of intoxication. It is thus noteworthy, that Van Hasselt incorporated general medical care into his handbook of toxicology. In doubtful cases, in which the international literature gave controversial results, he conducted own experiments, together with his 4th year students, using particularly the rabbit as experimental model. We may assume that he intended to improve his facilities for animal experiments at the RKMG, but in its budgetary meeting in 1867, the parliament waved his proposal. The incorporation of the RKMG into the Amsterdams Athenaeum Illustre (a public university college) was already in progress. Thus, he delegated his toxicological investigations with arrow venoms to the Physiological Laboratories, which were headed by prof. W. Kühne, a former student of Dubois-Reymond and Claude Bernard.

Van Hasselt was appointed as lecturer at the RKMG for the subject of toxicology officially in the period between 1842 and 1858, however, he was devoted to this topic for a much longer time. He had to obtain and complete his knowledge in toxicology as reader and by publishing. At the same time, toxicology experienced a rapid development, a change from casuistic descriptions to physiologically based insights, from empirical knowledge to an experimental scientific discipline.

The main objective of this thesis was to describe and evaluate the contribution of Van Hasselt to the field of toxicology. This question is not easy to answer, considering the fact that his limited scientific contributions are outweighed by his outstanding achievements as lecturer and author of numerous scientific contributions. With its detailed and well structured syllabi, textbooks and publications, Van Hasselt contributed significantly to the training and practical skills of military and civilian physicians. As civil servant he addressed various aspects relating to public health and initiated regulations devoted to the improvement of the public health services.

Finally, in his 'Second Career' he became an araneologist, with a national and international reputation.

**Addendum 1** presents an overview on the publications and other activities of Van Hasselt in a chronological order. In **Addendum 2** the contributions of Van Hasselt as araneologist are summarized. **Addendum 3** presents the recent understanding of the biosynthetic pathway of the various toxic plant secondary metabolites, mentioned in the preceding historical descriptions.