The heart in Down syndrome
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Preface and Outline of Thesis

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In 1866, J. Langdon Down published the results of his careful observations of the characteristic features of a group of patients, providing us with the first description of Down syndrome. However, it was not until 1957 that Lejune identified the underlying genetic mechanism responsible for Down syndrome. Lejune demonstrated that a third copy of chromosome 21 existed in these individuals. Today we know that the extra copy of chromosome 21 accounts for 95% of all cases of Down syndrome. Over the last 144 years, we have learned much about the intellectual, physical, and social development of persons with Down syndrome. Only within the last half century, however, significant progress has been made in improving the length of life of individuals with Down syndrome. With this extraordinary improvement in life expectancy, to around 60 years from the latest estimates, Down syndrome has been transformed from an acute condition with early death to a chronic condition with near-normal life span. As a consequence, management of the syndrome’s major health issues has become a significant concern. In addition to increased life expectancy, how we treat individuals with Down syndrome has changed.

This thesis
This thesis will address the heart in persons with Down syndrome. The main body of this thesis encompasses the treatment of pulmonary arterial hypertension due to systemic to pulmonary shunting in patients with a congenital heart defect. Aside from the studies concerning congenital heart defects, studies are presented investigating cardiac disorders in persons with Down syndrome without structural cardiac defects.

Outline
Chapter 1 gives an overview of the cardiovascular disorders in persons with Down syndrome from birth till adulthood. Thereafter this thesis is divided in 2 parts.

Part 1 concerns on Down syndrome, beginning with a theory-based demographic model to assess the prevalence of persons with Down syndrome (Chapter 2). Research tools are most often not adapted to persons with an intellectual disability. The six-minute walk test is commonly used test to measure submaximal exercise capacity (treatment effect) in patients with pulmonary arterial hypertension. In chapter 3, we investigate the validity and reproducibility of the six-minute walk test in persons with Down syndrome. Nowadays in most developed countries, all newborns with DS are evaluated for congenital heart defects by a
paediatric cardiologist and in case of a defect, followed by early corrective surgery, but this was not standard care before the 1980s. Therefore, a large group of particularly ‘older’ patients without early surgical repair are at risk of having complications of their heart defect. Chapter 4 presents the outcome of an echocardiographic screening in a particularly older population of persons with Down syndrome living in health care institutions. The following two chapters present the results of our research in regard to cardiac disorders in persons with Down syndrome without a congenital heart defect. First we report the presence of cardiac atrophy and diastolic dysfunction associated with inactivity. Next, we show that cardiac response to light exercise is decreased. In chapter 7, we present an interesting case of a female with Down syndrome and a mutation in the fibrillin-1 gene. We hypothesize that phenotypic expression of Marfan syndrome in our patient might be masked by the co-occurrence of Down syndrome.

Part 2 comprises studies on Eisenmenger syndrome. First, chapter 8 will give an overview of the past research on bosentan treatment in pulmonary arterial hypertension associated with congenital heart defects. We will present our research on the efficacy of bosentan in our patient population in patients with and without Down syndrome (Chapter 9, 10 and 11). Finally, we present the outcome of our national campaign about ‘missing’ adult patients with congenital heart defects in chapter 12.