Diabetic Retinopathy

A Cost-Effectiveness Analysis of Ophthalmoscopy and Photocoagulation

Diabetische retinopathie

een onderzoek naar de kosteneffectiviteit van fundusscopie en fotocoagulatie

proefschrift

ter verkrijging van de graad van doctor

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Nous ne pensons presque point au présent: et si nous y pensons ce n'est que pour en prendre la lumière pour disposer de l'avenir. Le présent n'est jamais notre fin. Le passé et le présent sont nos moyens, le seul avenir est notre fin.

Blaise Pascal, Pensées, II, 172

We rarely reflect on the present: and if we do so, we intend merely to obtain more insight into the future. The present is never our aim. The past and the present are only means, whereas the future is our ultimate destination.

Il est advenu aux gents veritablement sçavants ce qui advient aux espics de bled; ils vont s'eslevant et se haulsant la teste droicte et fiere, tant qu'ils sont vuides; mais quand ils sont pleins et grossis de grains en leur maturité, ils commencent à s'humilier et baisser les cornes: pareillement, les hommes ayants tout essayé, tout sondé, et n'ayants trouvé, en cet amas de science et provision de tant de choses diverses, rien de massif et ferme, et rien que vanité, ils ont renoncé à leur presumption, et recogneu leur condition naturelle.

Michel de Montaigne, Les Essais, livre II, chapitre XII
(Essais de Montaigne, Paris: Librairie Garnier Frères, 1925:(2)244)

True scholars experience what ears of corn experience: upright and proud, they grow and lift their heads as long as they are empty; but once mature, they carry the full and heavy grains of corn while their stems humbly begin bowing down-to-earth: similarly, men who have investigated and sounded everything and who have discovered nothing substantial and sure but emptiness in a mass of knowledge and a set of diverse affairs, will repudiate their presumption and recognise their natural condition.

To my father and my mother

Curriculum vitae

Harry Crijns werd 24 maart 1942 geboren te Heerlen. Na een studie macro-economie doceerde hij economie en informatica in diverse onderwijstypen. Sinds 1985 is hij verbonden aan de Erasmus Universiteit, waar hij tot 1988 was aangesteld bij de vakgroep *Informatica* (Faculteit der Economische Wetenschappen) en nadien bij het instituut *Beleid en Management Gezondheidszorg* (Faculteit der Geneeskunde en Gezondheidswetenschappen).

Preface

Early in 1990, prof.dr. A.F. Casparie entrusted me with a research subject that emanated from prof.dr. F. Hendrikse. Initially, I was inclined to consider the project with reserve and hesitation. Would an economist be able to contend fruitfully with questions originating from internal medicine and ophthalmology? After consulting a few articles, it became evident that full dedication would be indispensable to stand some chance of success. Because the articles allured me to this unfamiliar domain, the subject was explored by a brief literature study and a computer simulation. They revealed that a cost-effectiveness analysis of ophthalmoscopy and photocoagulation for diabetic patients requires components of several disciplines like computer science, economics, epidemiology, medicine, operations research and statistics. Anton Casparie and Fred Hendrikse were willing to supervise the production of the thesis and to assist in matters related to internal medicine and ophthalmology. Colleagues of the *Institute for Health Care Policy and Management* and the *Institute for Medical Technology Assessment, Erasmus University Rotterdam,* might give advice on other issues. This research subject gradually turned out to be a challenging gift. By the end of 1990, a new simulation for juvenile diabetic patients and a research report were ready. In February 1993, the Dutch version of the thesis was completed. The supervisors approved of it one month later. Thereafter, it was translated into English.

The production of this thesis has benefited from the support of several persons. By his numerous swiftly presented critical notes, Anton Casparie contributed substantially to create output of a better quality at a higher speed. Fred Hendrikse provided invaluable encouragement by his respectful attitude as well as his patience and clarity in explaining secrets of ophthalmology. In the future, the co-operation with Anton and Fred may continue. Prof.dr. F.F.H. Rutten kindly studied the preliminary and the final version of this thesis. By his remarks, Frans Rutten shielded me from important pitfalls regarding economic assessment. In co-operation with Fred Hendrikse, prof.dr. P.T.V.M. de Jong indicated how to translate aspects of the practice in ophthalmology into a model. Obviously, this support was indispensable. Paulus de Jong also contributed to this thesis by his justifiable scepticism regarding simulation models. Prof.dr. J. Verhoeff acquainted me with fundamental limitations of model building some years ago, when I enthusiastically worked in his department of computer science. Although Koos Verhoeff is at present creatively engaged in artistic computer

applications of mysterious beauty, he benevolently analysed the preliminary and the final version of this thesis.

Drs. H.J. Stoevelaar kindly helped finding data on disability facilities. Thanks to Herman Stoevelaar's suggestions, I could contact drs. B. Wouters (*Loo-Erf Foundation*, Apeldoorn, the Netherlands). From his practical acquaintance with rehabilitating visually handicapped persons, Mr Wouters generously provided worthwhile information on prices of disability facilities and on rehabilitation costs. Herman Stoevelaar also helped me to contact drs. J.A. Welling (General Director) and Mr P.A.M. Hendriks (Financial Director) of *Visio Foundation* for visually handicapped patients in Huizen, the Netherlands. They kindly presented details on costs, prices and government regulations regarding visual impairment and rehabilitation. Drs. B.M. van Ineveld submitted valuable ideas on discounting after reading an earlier version of chapter nine. Dr. B.A. van Hout presented literature suggestions on failure time analysis. Prof.dr. D.E. Grobbee provided support by analysing some chapters related to statistics and epidemiology. Drs. G.T. Koopmans entrusted me with a superior computer system which substantially facilitated developing the simulation model and writing the thesis. Mrs A. Ruys and Mr W. Meurs (Division Production and Invoicing, Financial Department, *Academic Hospital Sint Radboud*, Nijmegen, the Netherlands) kindly specified ophthalmic charges. Furthermore, the amiable help of the staff members of the Erasmus University's *Medical Library*, an oasis for researchers, contributed substantially to find publications on the research subject.

Drs. R.K. Buiter analysed the preliminary as well as the final version of the thesis. Rein Buiter kindly assisted me by his substantial expertise in statistics and by his ability to render enigmatic statistical topics transparent. Without his patience, it would have taken much longer to develop the rather new technique for the module *Disease Progression*, which is one of the principal components of the simulation.

Most unfortunately, it is no longer possible to thank the late drs. W.G. Jansen personally. For many years, Wim Jansen offered numerous chances for further development. He was the principal and indispensable *"catalyst"* of my graduating from secondary school teacher to university lecturer. A few days before he died, Wim advised to ask Mr R.F.R. Phillips, the former General Secretary of the *Economics Association* in the United Kingdom, to correct the English version of the thesis[1]. That may have

1 Mr R.F.R. Phillips corrected the translation of the parts A to F (pages 1 to 301). Mr Joseph McDonnell kindly checked the translation of the passages borrowed from Michel de Montaigne and Blaise Pascal (page iii). Want of time forbade to propound the remaining pages to MrPhillips.

been the most valuable of Wim's wise recommendations. As the difficulties of the English language forbid nearly all non-native speakers to attain fluency and stylistic elegance, Mr Phillips gave certainty that only an expert can provide. He received the English version in smaller bundles, which he always corrected and returned within a few days. His courteous and gentlemanly assistance was invaluable.

Although the previously mentioned contributions are very significant, they are overshadowed by the assistance of my parents. My farther and my mother have given me far more support than any son might normally expect from devoted and loving parents. They were always prepared to make substantial sacrifices for their children. Without their backing, I would never have been able to write this thesis. I have no words to express how deeply I feel indebted to them.

Finally, I thank Ella for accepting my spending many hours at the computer and Vendo de Louise Sainte-Claire for his surveillance of the keyboard as a Persian *"royal tiger"*. No other manager delegates duties as well as he does.

I hope that persons who I wrongly forgot to mention will accept my apologies.

Gouda, the Netherlands, September 28th, 1993

Contents

A

Introduction

1

Reconnaissance

Patients suffering from diabetes mellitus (DM) usually experience less distress from the disease itself than from the resulting chronic complications. These notably affect the heart, the brain, the blood-vessels, the nerves, the kidneys, and the eyes [CCEU 85; Nathan 86a; Verhoeven 89:14; Hendrikse 90:5; Orchard 90a; STG 91:33]. Complications of DM have a macro- or a micro-angiopathic character. The first category embodies coronary heart disease, cerebrovascular accident and peripheral vascular disease; the second category neuropathy, nephropathy and retinopathy [STG 91:32-3].

There are various data on the prevalence of chronic complications. Nevertheless it is obvious that retinopathy belongs to the most common complications [Krolewski 87]. The prevalence of diabetic retinopathy (DR) ranges from nearly 100% among younger onset diabetic patients (age at diagnosis < 30 years) who suffer seventeen years or more from DM [Klein 84b]. Amid older onset patients (age at diagnosis ≥30 years) prevalence reaches 95% and 70% [Klein 84c]. The first percentage relates to insulin taking patients, the second to patients treated with oral drugs or only with a diet. These maxima are reached some twenty years after the diagnosis of DM.

Retinopathy constitutes a serious threat to diabetic patients, especially to patients aged twenty to seventy-four years. The latter are twenty-five times more at risk for blindness than is the general population [AAO 89]. DM also causes a significant rise in mortality. The average life expectancy is cut by one third from the moment that DM is diagnosed [Veen 88; STG 91:30, 87]. Blindness among diabetic patients therefore concentrates on economically active age groups which usually contribute most extensively to production. Consequently both personal and social interests justify an investigation on how to combat this complication most effectively.

This is associated with primary, secondary and tertiary prevention. Different authors define these concepts differently. Some of these interpretations are discussed in sec-

tion 2.4. This thesis uses the distinction made by the *Steering Committee on Future Health Scenarios*. Primary prevention aims at preventing the incidence of DM, secondary prevention strives after discovering DM as early as possible, preferably before patients note symptoms, while tertiary prevention focuses at preventing complications or limiting their severity. This investigation confines itself to tertiary prevention. Regarding DR, primary, secondary and tertiary prevention are defined correspondingly, as indicated in chapter three.

Photocoagulation is the most important weapon in the battle against blindness caused by retinopathy. The treatment consists of focal or diffuse laser burns of the retina through the pupil. Investigations in the United States in the early eighties have proved that photocoagulation reduces the incidence of blindness resulting from DR by more than 50% [DRSRG 81; ETDRSRG 85]. The first publication relates to the treatment of proliferative diabetic retinopathy (PDR). The second deals with exudative diabetic retinopathy and macular edema, that both threaten the macula. The abbreviation ME in this thesis refers to both latter complications. The two investigations also demonstrate that the success probability of photocoagulation depends upon the condition of the retina. Section 3.3 presents further details on these disorders.

In less serious stages of retinopathy the expected benefits do not outweigh the damage caused by photocoagulation. However, when high risk DR develops treatment is required urgently because visual acuity may drop abruptly in that phase. The advantages then outshine potential harmful effects, because photocoagulation effectively reduces the probability of blindness [Ferris 87; Moss 88; Striph 88]. It is therefore most important to discover the need of treatment in due time [DRSRG 76; Blankenship 81; McMeel 81; Hendrikse 90:6; ETDRSRG 91b].

DR usually progresses slowly and rather predictably [Frank 84; Merimee 90; Frank 91]. However, patients experience the first symptoms of diabetic retinopathy, e.g. a significant loss of visual acuity, typically long after the appropriate time for treatment has passed [Klein 86a, 87a; Dasbach 91]. Regular eye examinations may provide ophthalmologists with adequate information for timely treatment. Both the quality and the frequency of these tests determine their reliability. A shorter screening interval may give ophthalmologists more information on the development of DR and provides more opportunities to correct an erroneous diagnosis. It increases the likelihood of timely discovering the progression towards a high risk state.

Facing these benefits, there are costs as eye screening requires the allocation of scarce resources. Scarcity in the domain of ophthalmic care not only refers to the definition

used by economists, who associate this concept with commodities and services for which the quantity demanded would exceed the quantity supplies at a price of zero [Lipsey 84:979]. Eye care in the Netherlands has to face a serious shortage of ophthalmologists [Biesheuvel-Snellen 90:5]. Hendrikse was in no doubt about this in his inaugural speech. After critical observations on budgetary constraints and bureaucracy he reaches a distressing conclusion.

> *The length of waiting lists for ophthalmic surgery has increased alarmingly in recent years. [Hendrikse 90:16]*

This speech furthermore presents an idea that is central to this investigation. Hendrikse argues that financial cuts in ophthalmic care will cause a significant rise of medical and social costs in the near future. Comparatively uncomplicated treatments with a rather promising probability of success cannot be performed because of waiting lists. Patients are not remedied before they reach the top of the waiting list. As a result of complications, they then require dramatically more expensive and more labour intensive care. The deficient resources are increasingly allocated to complex operations with a rather limited chance of success. As one patient requires more care, other patients have to wait longer. Eye care thus faces a vicious circle. The adverse personal effects are so evident, that they do not require discussion. As we know, the eye is the most important sense-organ. Eighty percent of all our knowledge is obtained through what we see. According to survey findings by the US Gallup organisation blindness is one of the most feared disabilities, second only to cancer [Goldstein 80:2-3]. In a Swedish study based on interviews 36 severely mobility-disabled subjects aged 24-52 years as well as 36 non-handicapped subjects rated the ability to see as the second most important function among 30 functions [Stensman 85].

The social-economic consequences of this course of events may be less manifest. How much productivity loss causes reduced vision? How many people become unsuitable for employment? What amount of social benefits is required? What is the cost of disablement facilities? How much vision can be saved after eye care is intensified? And what is the cost of incremental eye care? It would be immaterial trying to complete this incomplete list. The explorative investigation that preceded this study demonstrates that the two last questions provide enough substance to justify an investigation. Other questions therefore remain unanswered or are discussed only occasionally.

This beaconing creates close connections with diabetes mellitus and ophthalmology. For that reason the second and the third chapter present some concepts from medicine related to the subject-matter of this investigation. They regard DM, DR and photo-

coagulation. Chapter four explores whether a new study is justified. Chapter five completes the introduction and presents the central issues of this investigation followed by some observations on economic evaluation and a brief summary of subsequent parts.

2

Diabetes Mellitus

2.1 Introduction

DM is a chronic deregulation of metabolism caused by insulin deficiency or the diminished effectiveness of this hormone. Some patients suffer from absolute shortage, while others experience relative deprivation following an impairment in the body's ability to respond to insulin and insufficient insulin secretion [STG 91:18-9; Cejka 91:10; DeFronzo 92]. The term *diabetes* generally indicates DM. Strictly speaking this is not correct because diabetes refers to a set of metabolic diseases causing excessive secretion of urine. DM has by far the highest prevalence in this group. Therefore, diabetes *tout court* usually means DM [diabetes].

2.2 Pathogenesis

Digestion is the first phase of the metabolic process. Disacharides and monosaccharides, above all, are then split and the blood absorbs glucose while the blood glucose level rises. Normally this stimulates the islets of Langerhans - situated in the pancreas - to provide the blood with adequate quantities of insulin. This hormone enables glucose to leave the blood, to cross the membranes and to penetrate into the liver and muscle cells. Then the blood regains its normal glucose level. A shortage or a sub optimal utilisation of insulin deregulates metabolism so that an excessive quantity of glucose remains in the blood altering its chemical composition and creating higher viscosity.

These chemical changes affect some components of the blood, like the lymphocytes, hamper their functioning, reduce the transparency of membranes and increase the risk of complications in organs that receive insulin. The previous chapter mentions the most important complications. The accumulation of glucose in the blood increases the affinity between oxygen and haemoglobin. Consequently, the blood provides the organs

with smaller quantities of oxygen. The increased viscosity and the reduced flexibility of the lymphocytes obstruct the blood flow and delay the transport of nutritive substances, oxygen, warmth and waste material [Houtsmuller 91:53]. Eventually, this may cause some arteries and capillaries to deform [Frank 84, 91; Merimee 90]. The next chapter clarifies how the retina develops as a result of these alterations in the blood composition.

2.3 Subdivision

Pathophysiologically there are two main types of DM, namely type I and type II. The characteristic feature of type I is the absolute shortage of insulin caused by the sub clinical destruction of β-cells in the pancreas. Therefore type I is considered as an autoimmune disorder. Type II has a different nature. It results from a lessened insulin sensitivity of the body and a diminished secretion of insulin. The first phenomenon, insulin resistance, remains yet unexplained [Bruining 91:27-41]. The second event relates to the functioning of β-cells that supervise the glucose level of the blood continuously. At older age, the β-cells may work less effectively. Only at higher glucose levels in the blood, they then signalise the pancreas to raise insulin secretion and the glucose level of the blood apparantly gets a higher *"normal"* value. As the need for insulin seems to decrease, the secretion capacity of the β-cells ultimately diminishes. According to recent views, type II typically has the following pathogenesis [DeFronzo 92]. Insulin resistance is at the origin of this disorder. It augments the need for insulin. Initially, the pancreas is able to respond by increasing insulin secretion, so that type II is not yet manifest. However, after a while insulin secretion falls for reasons that yet remain unknown. The blood glucose level then generally reaches higher values and type II DM appears distinctly.

The abbreviation IDDM - *insulin-dependent diabetes mellitus* - stands for type I, as absolute insulin shortages are the hallmark of this variety of DM. Type II is denoted by the abbreviation NIDDM - *non-insulin-dependent diabetes mellitus*. IDDM and NIDDM are two distinct disorders each with its own aetiology and pathogenesis. Both afflictions may develop at practically any age [Krolewski 87]. Yet, the incidence of IDDM is concentrated in childhood, adolescence and early maturity, while NIDDM rather develops at middle or older ages. For reasons of convenience the age of incidence frequently provides the criterion to identify these types of DM. However, there is no universally accepted classification standard. Different investigators use different age criteria. To end confusion the *National Diabetes Data Group* - with members from Denmark, the United Kingdom and the United States - proposed in 1979 a classifica-

tion that does not refer to age [NDDG 79]. The proposal failed to reach its objective. Many prominent investigators still use the age criterion for practical reasons. Recent publications present the following limits: 17 years [Dorman 84], 17 and 20 years [Rewers 89], 20 years [Knatterud 83], 30 years [Palmberg 81; Klein 84b, 84c, 89a, 89c] and 39 years [Janka 89]. This thesis frequently uses the research results from Klein and associates. It therefore chooses the following limit. When the age of diagnosis is less than 30 years, patients are supposed to suffer from IDDM, otherwise from NIDDM.

The two groups also receive dissimilar treatment. Findings in the United States disclose, that over 90% of the younger onset patients - age of diagnosis <30 years - are insulin dependent. This applies to just 2% of the group older than 45 years [Huse 89]. Some investigators therefore consider type I and IDDM, as well as type II and NIDDM, as synonyms even when IDDM is distinguished from NIDDM by age. Older onset DM occurs 10 to 20 times more frequently than younger onset DM [CCEU 85]. Only a few juvenile diabetic patients are insulin independent. As compared to other juvenile diabetics, they demand less medical care, while they are at a smaller risk of developing complications. Just a handful of investigations focus on these patients. Available epidemiologic data seems too sparse for conducting a rigorous simulation regarding these patients. This investigation therefore distinguishes three groups of patients: (i) IDDM, (ii) NIDDM-a, standing for insulin taking NIDDM-patients, and (iii) NIDDM-b, not-insulin taking NIDDM-patients.

Some authors present pregnancy as another risk factor. Various findings exist on this subject. They relate to rather confined groups of patients [Stephen 63; Jervell 79; Klein 84d, 90a]. For that reason, the simulation does not examine this factor separately.

2.4 Prevention

Several investigators distinguish primary, secondary and tertiary prevention. The first concept generally indicates the occurrence of DM. According to Alberti [91] secondary prevention means averting the evil consequences of this disorder once it has developed. He regards tertiary prevention as the struggle against harmful effects of complications like exposure to pain and death. Another source considers secondary prevention as the successful fight against DM thanks to early diagnosis. In this view, tertiary prevention precludes worsening after the onset of DM [prevention].

Secondary prevention is alternatively seen as diagnosing DM soon after onset, whereas tertiary prevention relates to combating complications after they have developed definitely [STG 91:82]. Primary prevention precludes the onset of DR or delays the appearance of milder degrees of DR according to the *Diabetes Control and Complications Trial (DCCT) Research Group*. Secondary prevention obstructs the progression from milder to more severe types of DR [86]. It is unavoidable to make a choice between these definitions. However, there are no decisive arguments favouring one particular view, because each set of notions seems to offer interesting perspectives. The alternative proposed by the STG is arbitrarily selected as the reference point for this study.

Inheritance partially explains the development of DM and NIDDM in particular [Klein 84c; CCEU 85; Bingley 89; Blom 89; Dahlquist 89; Morris 89; Bruining 91:37]. Other risk factors, especially for NIDDM, are: older age, obesity, hypertension, elevated fat consumption, some food additives, less breast feeding, a higher age of the mother during pregnancy, infections, ethnical characteristics (Americans from Mexican origin are at higher risk than non-Hispanic whites, while the opposite holds for Asians and blacks), latitude (the incidence of IDDM in France and Italy is significantly lower than in the Netherlands, and higher in Scandinavia), and a lower social-economic status [NDDG 79; Cavender 84; Klein 84a, 84c; CCEU 85; Harris 87; Krolewski 87; Beaufort 88; Bingley 89; Hamman 89a, 89b; Wagenknecht 89; Bruno 90; Wingard 90; ADA 91; Haffner 91; Reitsma 91:24]. However, so far there is no consensus on the influence and weight of these factors [Blom 89; Haffner 90]. Modern medicine offers no technique to lower the incidence of DM. Primary prevention is impossible and there exists no treatment to cure DM.

It is interesting to note in passing, that DM reaches significantly higher prevalence levels in richer countries as compared to developing countries. This reflects diverging diagnostic criteria and methods, differences in the frequency of medical tests, another age composition, dissimilarities of life expectation and different social and nutritional habits [Reitsma 91:24].

Secondary prevention, in other words early diagnosis to hinder complications, is immaterial as to IDDM because this type of DM is clearly manifest from the moment of onset. For NIDDM secondary prevention has greater importance. In the United States only half these patients seem to be diagnosed [Harris 87].

Tertiary prevention, meant to deter complications from occurring or worsening, offers at present far brighter perspectives than primary or secondary prevention. There are three techniques to control metabolism: (a) diets, (b) oral medication and (c) insulin

injections. The first treatment suits the mildest type of DM, the last the severest. Until 1921, when Banting and Best succeeded to produce an insulin extract, the insulin dependent type caused death within one or two years after onset. Insulin injections have increased the life expectation of IDDM patients ever since. They enable approximately normal metabolism, even for patients who suffer from the worst kind of DM. Moreover, medical technology by now provides reliable, compact and easy to use instruments for self blood glucose monitoring. Several investigators have discovered substantial evidence indicating that proper metabolic control reduces the risk of late micro-angiopathic complications significantly [Pirart 78a, 78b; Tchobroutsky 78; Reitsma 83; Klein 88a]. Photocoagulation is obviously part of tertiary prevention. It will be considered later in this publication.

2.5 Incidence and Prevalence

DM gains more and more ground. To a considerable extent, this is due to the success of medical technology. As life expectation increases, older ages expose more people to relatively high incidence rates of NIDDM. For the same reason, more children may have one or two parents who suffer from DM. This enlarges the weight of the risk factor inheritance.

The progression of DM in Western countries also results from recent demographic developments. The decline of natality in previous decades alters the age composition. The share of older age groups increases, while younger age groups become relatively less numerous. Consequently, this demographic process leads to a higher number of NIDDM cases, while the number of new IDDM patients falls. In older age groups, the relative incidence of DM is significantly higher than in younger age groups. Therefore, the prevalence and the incidence of DM rise [Palumbo 76; Melton 83a; CCEU 85; STG 91:5, 27]. Given the existing age composition, the population will age in the next decades. The ground gaining by DM may therefore be seen as a lasting phenomenon.

Still, this excites comment. Along with the demographic changes, autonomous movements contribute to a higher prevalence of IDDM [Stewart-Brown 83; Vaandrager 84; Krolewski 87; Bingley 89; Joner 89; Keiding 89; Rewers 89; Bruining 91:28]. Furthermore, there is the influence of economic factors. A higher purchasing power in industrialised countries causes nutrition patterns to change and fat consumption to increase. As a result, more people become obese and are at greater risk of developing NIDDM [Mann 83; Lipson 86].

The higher incidence and prevalence of DM, notably NIDDM, also follow from (i) improved diagnostic techniques, (ii) more frequent tests of risk groups and (iii) modified diagnostic criteria. The first issue refers to cheaper and more advanced measuring instruments that enable general practitioners to discover DM more efficiently. The second issue relates to the current state of urbanisation, transportation, real income and the financing system of health care in European countries. It is plausible, that these factors have lowered thresholds, so that risk groups are examined more frequently. However, this relationship is rather complicate and lies beyond the scope of this investigation. It will not be discussed any further. Regarding the third issue, the effect depends on the direction in which diagnostic criteria change. Patients with impaired glucose tolerance, for example, are no longer diagnosed as diabetics according to the latest criteria of the *World Health Organisation* [Verhoeven 89:8].

What does this evolution imply for the Netherlands? Virtually every factor points at increasing prevalence, as the following prognosis by the *Steering Committee on Future Health Scenarios* affirms. The numbers for 1990 are estimates.

Year / Demographic scenario	1980	1990	2005	1990-2005 Growth	
				Absolute	%
Static variant	191,000	222,000	271,000	49,000	22
Dynamic variant	191,000	242,000	339,000	97,000	40

Table 2.1 - Expected number of DM patients in 2005 in the Netherlands [STG 91:5]

Both the static and the dynamic variant of the prognosis for 2005 are based on the expected size and composition of the population in the Netherlands. The static variant postulates constant age and sex specific prevalence rates corresponding to data from 1980. By contrast, the dynamic variant uses a more advanced computation method as it assumes incidence rates to remain constant. This technique gives room to relate the prevalence of DM to the changing age and sex composition of the population. Additionally, the dynamic model assumes, that the onset of DM reduces life expectation by a fixed fraction [Hoogenveen 90:15-20]. In this way, the dynamic model presents a more refined approach than the static model.

In the near future substantially more people in the Netherlands, as in other Western countries, will fall victim to DM and its complications. The next chapter briefly reviews the complication that makes up the key subject of this investigation: DR.

3

Diabetic Retinopathy

3.1 Introduction

Metabolic disturbances typical of DM may provoke various complications in the human eye, like cataract and glaucoma in the anterior part and retinopathy in the posterior part. Lens opacity that seriously affects vision characterises cataract, while glaucoma is a condition in which the intraocular pressure is raised to abnormal levels following obstruction of the flow of aqueous humour through the pupil to the anterior chamber. These eye diseases become progressively more common with advancing age [Klein 84e; Morse 86]. Retinopathy is a general term for retinal disorders, that may be distinguished according to their nature, severity and position. Further discussion on this topic follows later on.

As mentioned earlier, the prevalence of retinopathy reaches high ceiling values among diabetic patients: IDDM ±100%; NIDDM-a ±95%; NIDDM-b ±70% [Klein 84b, 84c]. The discovery of insulin extracts has increased the life expectation of insulin dependent patients significantly. Therefore, the wider spread of DR is considerably related to this group of patients. In the United States the proportion of the recorded incidence of blindness attributed to DR was less than 1% in 1930. It increased to 15% in 1960 and to 23% in 1980. At present, DR is the leading cause of blindness among Americans aged 20 to 74 years [AAO 89; L'Esperance 90:667].

3.2 Pathogenesis

Numerous investigations indicate, that hyperglycaemia significantly contributes to the incidence and worsening of DR. According to a study by Janka and associates the incidence risk of severe types of DR increases considerably as a result of abnormally high blood glucose levels [89]. During a four-year follow-up 2.9% of the patients with

haemoglobin A_{1c} (HbA_{1c}) levels <8.4% progressed from minimal background DR to preproliferative or proliferative DR, whereas 44.4% of the patients with HbA_{1c} ≥9.9% had to endure the same progression. An investigation by Klein and associates reaches virtually the same conclusion [88a].

Frank, however, questions this relationship. In his recent review on the pathogenesis of DR he states explicitly, that there is yet no definitive proof that chronic hyperglycaemia constitutes the basis of DR [Frank 91]. This is remarkable, because he indicated chronic hyperglycaemia a few years earlier as the most important risk factor for DR [Frank 84]. From these contradictory views we now examine some explanations of the development of DR.

An investigation by Kohner and associates [82] focuses on hypoxia. At abnormally high HbA_{1c}-levels haemoglobin holds oxygen longer. Therefore, the heart has to generate a larger blood flow to supply the retina with adequate amounts of oxygen. This may explain microvascular abnormalities and leakage, as well as neovascularization. The reduced deformability of erythrocytes may bring about the same phenomena [Houtsmuller 91:53]. Under normal circumstances erythrocytes with a diameter of 8µ can cross capillaries not wider than 3µ thanks to deformation. Prolonged elevated blood glucose levels harden the erythrocyte membrane causing congestion and obstruction at the entrance of capillaries. They no longer receive enough oxygen and meanwhile they also accumulate a surplus of waste matter. The retina may react spontaneously by neovascularization to enable the blood flow to pass through.

A study by Merimee [90] distinguishes several phases in the development of DR. Biochemical alterations related to hyperglycaemia predominate during the first phase. Through protein cross-linkage they cause the thickening of membranes and capillaries. The functioning of pericytes and endothelial cells then changes and the patency of retinal vessels diminishes. In the second phase, haemodynamic mechanisms are preponderate in the view of Merimee. Elevated blood glucose levels provoke a higher blood viscosity that strains the heart, the arteries and the capillaries because it results in increased friction between the blood flow and the membranes. This may damage the endothelium of the vessels and induce protein leakage that causes hard or soft exudates. Consequently, the retina suffers from insufficient blood supply, oxygen shortage and alterations due to hard exudates. In the third, and most severe, phase Merimee emphasises the role of endocrine factors. The growth hormone IGF-I (insulin-like growth factor I) may then contribute to neovascularisation by inducing the expression of the glucose-transporter gene and by stimulating cellular proliferation. However, the

relation of IGF-I to DR is only partially known. Furthermore it is quite probable, that there are incentives for neovascularisation in areas with capillary retinal occlusion.

It would be incorrect to conclude, that the factors mentioned in the previous paragraph characterise the development of DR in one phase only. The opposite is true. These factors affect the whole process, although some factors are predominant in each specific phase. After this investigation, Merimee is unable to prescribe a therapy. However, he is quite convinced, that hyperglycaemia is the most consistent derangement in this process. Physicians should therefore control hyperglycaemia as effectively as possible. A study among Mexican NIDDM-patients comes to similar conclusions [Paisey 84a, 84b].

Other investigators also present findings that point to a positive correlation between the blood glucose level and the incidence or worsening of DR [Pirart 78a, 78b; Howard-Williams 84; Krolewski 86; Teuscher 88]. However, this relationship requires a more balanced appraisal. A positive correlation seems correct, as long as patients do not suffer from DR. However, once DR has developed, the relationship is no longer significant [Engerman 87]. In passing it is worth noting, that effective metabolic control has a serious drawback, because it increases the risk of severe hypoglycaemia[Amiel 87; Clarke 91; Meijer 92].

Apart from that, the comparison of all investigations on the relationship between metabolic control and the incidence and pathogenesis of DR would require a separate analysis. Until 1987, the results were published of more than 400 studies on this subject [Goldberg 87]. Roughly one half points to a significant relationship, while one out of three studies does not discover any significance. Goldberg presents no opinion upon the remaining investigations. As this relationship can only be treated briefly in this context, just a few well known findings have been presented to illustrate current insights. Hopefully, the ongoing large scale investigation by the American *National Institutes of Health* will present more certainty on this relationship in the second half of this decade. It carries the title *Diabetes Control and Complications Trial (DCCT)* and follows patients up to 10 years [DCCTRG 86].

3.3 Subdivision

As mentioned earlier, disorders in the retina may be distinguished according to their nature, severity and position. The classification, that follows shortly, primarily illustrates the first two criteria. The importance of the third criterion relates to the structure

of the retina. It embodies a central and a peripheral part. The macula is situated in the centre, where the central fovea holds a vast number of densely packed light-sensitive cones for accurate vision. By contrast, the density of light receptors is considerably lower in peripheral areas of the retina. Clinical practice reveals, that mild peripheral abnormalities less frequently cause visual disorders. However, disorders of similar severity are far more likely to threaten vision, if they are situated in or near the macula. The following two facts support this. First, the condition of the macula largely determines the quality of central vision. Second, peripheral areas cover a far larger surface so that a disorder of a certain magnitude causes comparatively less damage in the periphery than in or near the macula.

Now that the aspect *"position"* has been dealt with briefly, the factors "n*ature"* and *"severity"* will be discussed on the basis of some well-known classification schemes. In doing so one should remember, that DR comprises several disorders that different patients may endure at different moments of time with different intensities. It is difficult to capture this complex pathogenesis in a frame of unambiguous concepts that prevent misunderstanding. It is quite conceivable, that the same notion gets different definitions in different studies.

To avoid confusion American, British and Scandinavian physicians arranged a consensus meeting in 1968 that resulted in the *Airlie House* classification. This still is the point of reference for several publications [Klein 84b; Goldberg 87; ETDRSRG 91b]. The *Early Treatment Diabetic Retinopathy Study (ETDRS)* distinguishes thirteen levels. The first indicates the absence of DR. The five following levels specify certain grades of mild non-PDR, or non-proliferative DR. Microaneurysms (slight dilation of the venules) and haemorrhages are typical characteristics of the mildest grade of non-PDR. Hard and soft exudates (material that has passed through the walls of vessels into adjacent tissues or spaces, especially in inflammation), intraretinal microvascular abnormalities and larger patches of haemorrhages appear, when the severity of mild non-PDR increases. The last seven levels of this classification relate to various grades of PDR, when preretinal neovascularisation and glial proliferation occur. PDR may lead to haemorrhage into the vitreous and traction on the unsupported new vessels from the vitreous jelly. Ultimately, this can totally impede the functioning of the retina and provoke retinal detachment [ETDRSRG 91b].

The epidemiologic study of DR in the American state Wisconsin initially distinguished eleven levels. Each eye was classified separately [Klein 84b]. Later on, for practical reasons the number of levels was reduced to eight [Klein 86b]. The application of such classification scheme presumes that internists and ophthalmologists, among others,

generally accept some widely known fundus photographs as a reference standard. However, only a limited number of professionals are sufficiently acquainted with this classification and so the scheme can hardly foster professional communication [Peperkamp 91:146]. Investigators usually use a few broader categories: (i) mild non-PDR, (ii) pre-PDR and (iii) PDR [Verhoeven 89:34; L'Esperance 90:668]. Some authors also distinguish exudative DR from macular edema, that threaten the macula [Bresnick 86; Kinyoun 89]. In this publication the abbreviation ME indicates *both* exudative DR and macular edema.

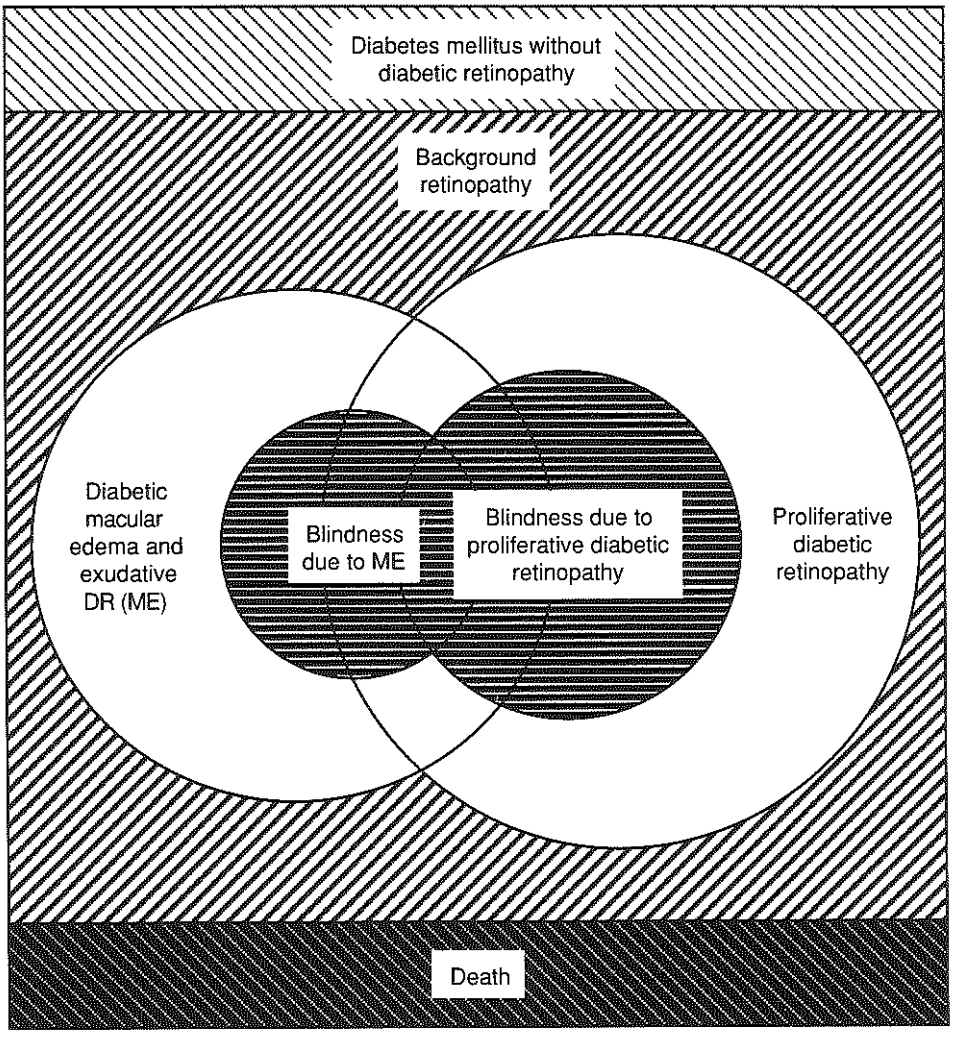

Figure 3.1 - Schematic classification of DR and vision loss

Following Javitt and his associates [89, 90] together with Rohan and his associates [89], this investigation chooses an even cruder classification presented in figure 3.1. It is based upon the division of the retina into two areas: (i) the centre or macula and (ii) the periphery. For reasons of convenience the latter will sometimes be called *"retina"*, indicating the whole retina except the macula. This study specifically examines the effectiveness of photocoagulation. In this context it is adequate to recognise two conditions for both areas, namely a phase when photocoagulation is not yet indicated and another phase when it is. The simulation distinguishes: (i) background retinopathy, abbreviation BR, (ii) ME and (iii) PDR. BR refers to milder conditions of DR. In eyes that only suffer from BR the benefits of photocoagulation do not outweigh the risks (slight vision loss, reduced night vision and laser scars). ME is an indication for focal or a grid photocoagulation of the macula, while PDR requires panretinal or scatter photocoagulation of the peripheral retina.

It may seem self-evident to consider BR as a broad category, that encloses the five levels in the ETDRS classification scheme designated as pre-PDR. But this is only partially correct. In the simulation the indication of photocoagulation occupies a central position. At present, this indication roughly coincides with the moment when PDR appears, as far as the periphery is concerned. In the future, however, technological improvements may shift the moment of indication, for instance towards an earlier phase in the development of DR.

From this perspective BR may be seen as a set of health conditions characterised by the presence of minor grades of DR, that do not yet require laser treatment. Technological advances determine the boundaries of this set. In future the set may become smaller and correspond to non-PDR as defined by L'Esperance and Verhoeven. Panretinal photocoagulation would then be indicated in the phases of pre-PDR and PDR. This approach serves two purposes. First, the vocabulary of the simulation model should agree with reality. This makes it easier for clinicians to understand and check the functioning of the model. It may hinder the model to drift away from the ophthalmic clinical practice. Second, this terminology makes it possible to follow technological changes that affect the point where photocoagulation is indicated.

3.4 Primary Prevention

The fight against DR requires insight into its most important risk factors. Although these have been the subject of many investigations, there exists no consensus yet, particularly regarding the impact of blood glucose levels. However, notwithstanding con-

sensus most studies point into a certain direction. The duration of DM usually appears to be the most important risk factor for the incidence of DR [Pirart 78a, 78b; West 82; Klein 84b, 84f, 87b; Nielsen 84; Paisey 84a, 84b; Burger 86; Nathan 86a; Weber 86; Krolewski 87; Haffner 88; Cerutti 89; Chase 89; Nelson 89; Kalter-Leibovici 91]. As mentioned earlier, hyperglycaemia is another important risk factor according to several investigators [Pirart 78a, 78b; West 82; Howard-Williams 84; Klein 84b, 84f, 88a; Paisey 84a, 84b; Rand 85; Krolewski 86; Nathan 86a; Weber 86; Haffner 88; Teuscher 88; Cerutti 89; Chase 89; Janka 89; Merimee 90; Orchard 90b; Kalter-Leibovici 91]. Age is usually put forward as the third risk factor.

The preceding bibliographical references indicate, that many investigators agree on three risk factors: duration of DM, metabolic control and age. Moreover, they mention these factors in the same order of decreasing importance, emphasising that the duration of DM is the most influential risk factor. Some studies also state, that hypertension increases the probability of DR [Paisey 84a, 84b; Teuscher 88; Janka 89; Klein 89b; Chase 90]. Furthermore, the prevalence of DR relates to medication. Insulin taking NIDDM-patients are at higher risk than other NIDDM-patients [West 82; Klein 89a; Nelson 89].

Nevertheless, these findings excite comment. NIDDM is as such a risk factor for the incidence of DR. Patients taking insulin generally face more severe grades of NIDDM as compared to patients that use drugs or follow a diet. The worsening of NIDDM therefore increases the probability of both insulin taking and DR. Furthermore, insulin taking may be a risk factor by itself. Each method of external metabolic regulation may cause temporary derangement for instance when a patient unexpectantly deviates from his normal eating habits or endures abnormally heavy bodily strain. In case external metabolic control should be more drastic, the automatic regulation of metabolism from within the body has become relatively less important. External regulation, however, cannot fully match the fine tuning that the pancreas realises in normal metabolic conditions. Consequently, insulin taking reflects an increased likelihood of metabolic abnormalities as compared to other types of medication.

The higher prevalence of DR among insulin taking NIDDM patients also results from more severe metabolic disturbances, assuming these are risk factors. Furthermore, insulin taking NIDDM patients have a significantly higher average duration of DM [Klein 89a]. One may therefore wonder, whether insulin taking must be considered as a separate risk factor. A longer duration of DM may involve further devastation of β-cells, increased insulin resistance and reduced insulin sensitivity.

Hereditary factors and obesity should also be mentioned [NDDG 79; CCEU 85; Leslie 86; O'Rahilly 88; Morris 89; Mykkänen 90; Bruining 91:38]. The influence of obesity is questioned though [Haffner 90]. The probability of DR further relates to the age of onset of DM: the lower the age of onset, the higher the likelihood of DR. Yet, DR seldom occurs in childhood [Parving 88]. There also exists a positive correlation between macro and micro vascular complications [Hiller 88]. Finally, patients with low or undetectable plasma C-peptide levels or increased cholesterol levels are at greater risk of developing DR or PDR [Klein 90a, 91a].

Some of these risk factors may be regulated. But it is impossible to steer the principal factor, the duration of DM, and the third factor, age. Clinical practice demonstrates that some factors, e.g. metabolism, can be influenced substantially, but nevertheless partially. Primary prevention has limited importance. Frank [86:956] presents a far more outspoken statement: *"No medical therapies have proved to be effective against diabetic retinopathy"*.

3.5 Secondary Prevention

Several years may elapse between the onset of DR and the moment, when patients perceive the first symptoms. Often, patients do not complain of DR, until this disorder reaches the stage of ME or PDR. Vision loss is typically the earliest apparent manifestation of ME. Preretinal haemorrhages make many patients for the first time aware of PDR, following serious midperiferal retinal abnormalities that develop unnoticed [Peperkamp 91:142-3]. Therefore, perceptions by patients are not well suited to diagnose DR on time. They make up a flimsy basis for secondary prevention. Moreover, they offer little support for the fight against blindness among diabetic patients. As explained later, effective treatment requires scrupulous watching of the onset and the development of DR. Diabetic patients should have frequent eye examinations considering the importance of adequate secondary prevention [Blankenship 81; Porta 91; RWP 91]. Who should perform these examinations? How should they be accomplished? How frequently should they be done? In this context, the answers must be confined to matters that are relevant to the simulation.

The optimum that modern ophthalmology can offer might look the most obvious standard. However, several barriers put this optimum out of reach. Some of them relate to the financial means of patients and the availability of ophthalmic care. Others concern health care in general or ophthalmic care in particular, notably the shortage of ophthalmic care in the Netherlands. These obstacles explain why a considerable num-

ber of patients are not examined with adequate frequency [Klein 90c]. A study of IDDM patients in Wisconsin, United States, reveals that 22% never have an eye examination, 26% at best biannually and 52% at least once a year [Dasbach 91]. An investigation by Verhoeven [89:70] in four general practices with some 12,000 patients in Heerde (Gelderland, the Netherlands) points to a similar situation. Among 136 NIDDM patients exactly 50% have an eye examination once every three years. The other half are checked less frequently, some of them never.

However, not only ophthalmologists perform eye tests. One might wonder, whether this is desirable. An investigation in three centres in the United Kingdom by Buxton and associates [91] reveals, that the performance of primary screeners in ophthalmoscopy varies from 41% to 67% with respect to sensitivity and from 89% to 96% regarding specificity. Clinical assistants' referral grades form the reference standard against which these rates are assessed. A study in the region of Enschede, the Netherlands, leads to similar findings: general practitioners who lack specific training do not seem fully competent to diagnose DR [Huiskes 91]. And under optimal conditions internists and diabetologists in two American university-affiliated hospitals miss the diagnosis of PDR in 49% of the cases [Sussman 82]. Consequently at present, the tracing and watching of DR should preferably be entrusted to ophthalmologists.

Nevertheless, certain arguments argue for a different approach, at least to a limited extent, because Nathan and associates [91] found, that well-trained diabetologists can be as effective as ophthalmologists in determining the severity of DR. Furthermore, some patients may not have eye examinations at all as a result of bottlenecks in ophthalmic care. For pragmatic reasons it then seems sensible to have recourse to less accurate screening techniques. They enable diagnosing at least some patients in the group where DR might otherwise remain unnoticed. Apparently, the United Kingdom faces such a situation, as the density of ophthalmologists is considerably lower than in the Netherlands, namely one per ± 93,300 inhabitants versus one per ± 39,000 [1]. This ratio is, however, less favourable in the Netherlands than in France (1 : ± 13,300), Belgium (1 : ± 16,600) or Germany (1 : ± 17,700). Therefore, it is easy to understand, why alternative screening techniques are being tested in the United Kingdom. Well-known are mobile screening units for non-mydriatic Polaroid retinal photography. This technique gives patients in peripheral areas wider access to ophthalmic care. However, there are contradictory findings on the quality of these tests. Williams and associates [86] report a sensitivity of 84% and a specificity of 99.5%, as compared to an oph-

1 source: Dr. Rolf Grewe (Münster 1989) [quoted in: NOG 92:16] The shortage of ophthalmologists in the United Kingdom is partially compensated by the availability of highly qualified opticians.

thalmologist's clinical assessment. Taylor and associates [90] claim, that this screening method *"is at least as good as ophthalmoscopy with mydriasis in routine diabetic clinics in identifying new vessel formation and absence of retinopathy and is significantly better in detecting exudative maculopathy"*. According to the findings by Chantelau and associates [89] one photograph per patient is sufficient. The assessments by Klein and associates [85a] as well as by Buxton and associates [91] are moderately positive. A recent investigation by Sculpher and associates concludes, that considerable cost savings can result, if systematic screening, with a combination of different screening technologies, is to be superimposed upon a well-organised system of general diabetic care at the general practice [92].

As opposed to this, Jones and associates [88] find, that pre-proliferative and proliferative abnormalities are overlooked on these photographs, whereas ± 20% of the photographs are useless. The study by Moss and associates [85] is also relevant in this setting. Contrary to the investigations presented in the previous paragraph, seven-field stereoscopic colour fundus photography constitutes the reference standard to assess the effectiveness of eye examinations. Ophthalmoscopy has a sensitivity of 79.4% and a specificity of 98.9% in discovering high-risk proliferative lesions [Dasbach 91]. Yet, ophthalmoscopy is the reference standard in the studies by Williams, Taylor and their associates.

In the Netherlands mobile fundus cameras have few protagonists, although the cost-effectiveness of mydriatic fundus photography has been investigated[2]. There exists a relatively larger supply of ophthalmic care than in the United Kingdom, so that the need for alternative screening methods is less urgent. The differences between the Netherlands and the United States mainly regard the geographical and financial access to eye care. Patients in the United States live on average further away from the nearest ophthalmic clinic because of a lower population density. Therefore, American patients spend more time and money on their way to eye examinations. Moreover, in 1977 21.9% of the working poor in the United States, with a household income less than

2 This investigation was carried out by: (1) the Department of Ophthalmology, De Weezenlanden Hospital, Zwolle, the Netherlands; (2) S. Verhoeven MD, PhD, general practitioner, Heerde, the Netherlands; (3) Institute for Health Care Policy and Management and (4) Institute for Medical Technology Assessment, Department of Medicine and Health Sciences, Erasmus University Rotterdam, the Netherlands. The study compares ophthalmoscopy to fundus photography. Pupils are dilated in both screening methods. Out of 643 type II patients examined by fundus photography 217 patients were selected at random for an ophthalmoscopic examination immediately afterwards. These screening methods have a significant measure of agreement regarding referral recommendations: $\kappa = 0.54314$; t-value = 8.13408 [Loeve 92:93].

1.25 times the poverty line, lack health insurance while 10.1% of the population age 16–64 years have no health care insurance {Berk 87]. This also applies to 12% of the diabetic patients in that age group [Taylor 87].

Only one out of every three poor receives *"Medicaid"*. After 1977 the situation deteriorates. From 1977 to 1982 the number of poor increases by some 8 million and 2.4 million persons are no longer entitled to *"Medicaid"* benefits subsequent to more restrictive eligibility criteria. In 1987 some 37 million inhabitants of the United States - ±15% of the general population - have no health care insurance [Glaser 89]. Data for 1985 indicate, that the proportion of uninsured reaches a maximum amid unemployed persons (41.4%) and a minimum in the full time employed group (9.4%) [USGAO 88]. In 1991 90,000 persons in the Netherlands - 0.6% of the general population - lack health care insurance [CBS 92a:18]. Many uninsured inhabitants renounce insurance for religious reasons. The Dutch study, mentioned in the previous paragraph, therefore primarily relates to the quality of eye examinations.

It does not follow, however, that patients in the Netherlands enjoy optimal access to eye care. The previously mentioned study in Heerde reveals, that many diabetic patients do not have enough eye examinations. A study in Hoogeveen, Drenthe, the Netherlands, reaches a similar conclusion [Reenders 91]. The last investigation also shows, that fundus photography is rather expensive and causes discomfort, especially for elderly patients, unless mobile screening units are used. From this study it follows furthermore, that the effectiveness of ophthalmoscopy decreases, if this test is delegated to general practitioners. This examination requires practice, but the confined prevalence of DR prohibits general practitioners to get enough routine, even if they receive in-service training. Consequently, ophthalmoscopy by ophthalmologists is likely to remain by far the most important screening technique in the Netherlands in the near future, although some findings justify transferring a few duties to general practitioners [Kar 88:101].

Besides ophthalmoscopy and fundus photography, fluorescein angiography enables the examination of retinal disorders. This technique is notably superior in assessing the leakage of retinal vessels in the macular area [L'Esperance 90:675; Ivanisevic 90]. However, it is quite time consuming, expensive and imposing [Peperkamp 91:145; Reenders 91:48]. This simulation therefore remains restricted to ophthalmoscopy by ophthalmologists, though with one exception. Before laser treatment the retina of some patients is evaluated with fluorescein angiography. This will be discussed later on.

3.6 Tertiary Prevention

Various techniques have been tried out to combat the progression of DR: pancreas transplantation is one of them. This operation relies upon the observation that the malfunctioning of the pancreas, especially among juvenile diabetic patients, provokes metabolic abnormalities which promote the incidence of DR and other complications. A successful operation destroys the root of all this evil. Up to July 1988, at least 1,500 pancreas transplants had been reported world-wide, the majority of which were simultaneous pancreas and kidney transplants (1984-1988: 66%) [Sutherland 90:869-73]. A recent study of eight transplants plus four controls produces no evidence for significant differences in the development of DR [Petersen 90]. These results, however, may be questioned. The investigation comprises a small number of patients most of whom have to face advanced DR that excludes substantial regression [Frank 90; Sutherland 90:876]. In the near future, only a limited minority of all diabetic patients will have a pancreas transplant [STG 91:103]. This comparatively expensive treatment[3] can only be given in cases where adequate donor organs are available. Moreover, some 7% of the patients die within one year after the transplant [Sutherland 90:875].

Photocoagulation is a far more promising technique. It involves the channelling of a light beam through the dilated pupil to a specific spot or area in the retina. As the light beam strikes the retina, the temperature may reach 10,000°C. A coagulum is formed which can destroy micro aneurysms, leaky retinal vessels, areas of retinal edema or capillary micro infarction. Moreover, this treatment may contribute to maintain a more normal development of the retina.

Meyer-Schwickerath introduced photocoagulation in 1949 using sun-rays. Six years later, the xenon-arc light bulb was unfolded as an alternative, making photocoagulation independent of atmospheric conditions. L'Esperance presented argon photocoagulation in 1968. As this technique creates finer coagula, it enables the treatment of areas nearer the macula. Moreover, this procedure is in most cases performed without anaesthesia [Hendrikse 90:10-1; L'Esperance 90:674]. Yet, there is only partial consensus. Some ophthalmologists have found evidence, that the xenon technique is more effective [Okun 84]. Nevertheless, argon has at present by far the broadest dispersion [Vondeling 93].

3 Indication: A kidney transplant now costs some *f* 75,000 [Ancona 92:17].

Initially, ophthalmologists applied photocoagulation reluctantly. This is self-evident. Until now, the reason why this type of therapy slows down, or blocks, the progression of DR remains partially unveiled [Hendrikse 90:13; L'Esperance 90:675]. Nonetheless, even early applications of photocoagulation offered substantial evidence in favour of this therapy. Untreated eyes proved more likely to become blind than treated eyes. Is this dissimilarity significant?

This was the central issue of a large-scale randomised investigation in the United States, that the *Diabetic Retinopathy Study Research Group (DRSRG)* started in 1971. It concerned 1,758 patients suffering from PDR in at least one eye or from pre-PDR in both eyes. One eye was selected at random for laser treatment. Half the designated eyes were treated with argon laser equipment, the other half with xenon. The first results appeared in 1976 [DRSRG 76], over two years after the treatment of the first 354 patients. Blindness (visual acuity <5/200 [4]) had developed in 16.1% of the untreated eyes and in 5.1% of the treated eyes. More recently treated patients offered a similar picture, but the contrast was less striking. The differences between argon and xenon did not prove to be significant.

In 1981, following several interim reports, the DRSRG [81] published results that conclusively confirmed the effectiveness of photocoagulation in treating PDR. The probability of severe vision loss decreased by 50% or more in the first two years after the treatment of eyes with neovascularisation and preretinal or vitreous haemorrhage. Similar evidence emerged for eyes with neovascularisation equalling or exceeding 1/4 to 1/3 *"disc diameter"* and situated on or within one *"disc diameter"* (∅ 1.5 mm) of the optic disc. Other investigators have confirmed these results thereafter. In a small-scale study of 50 eyes with PDR, a clear distinction emerged just a few weeks after treatment. Some eyes responded positively, while the treatment turned out to be far less effective in other eyes. This early distinction was a significant predictor of the development during the first six months [Doft 84]. Another publication concerned 351 eyes, without controls, that were tracked for five to twelve years after photocoagulation [Little 85]. The author qualifies the results as excellent, provided the treatment is repeated from time to time. Unfortunately, the publication presents no information on the frequency of follow-up treatments.

Fifteen medical centres in the United States participated in the DRSRG investigation. For one of these centres, Blankenship [91] presents results regarding 51 patients 15

4 There are numerous definitions of blindness. Section 7.3 indicates which definition applies to this simulation. The same section presents measures of visual acuity.

years after they received laser treatment. Visual acuity was less than 20/200 in 7 (14%) treated and in 21 (41%) untreated eyes. Although the number of patients is too limited to draw definitive conclusions, this evidence suggests, that photocoagulation also reduces the risk of visual loss in the longer run. Argon seems marginally more successful than xenon. On the other hand, panretinal photocoagulation generates retinal scars that weaken night and peripheral vision. Consequently, these investigations raise new questions. Which phase of DR offers the most favourable conditions for maximising the effectiveness of photocoagulation? When should focal photocoagulation be applied rather than panretinal photocoagulation? Can laser treatment combat visual loss caused by ME?

In 1980 the ETDRS started a large scale study on the effectiveness of photocoagulation in eyes with ME. In 29 centres 1,876 out of 3,928 patients were selected. The investigation included 2,998 eyes, as 754 patients had only one eye examined. Immediate argon treatment was given to 1,508 eyes: 754 panretinal and 754 focal. The control group - 1,490 eyes - received photocoagulation later on. One, two and three years after treatment eye tests revealed, that focal photocoagulation reduces the risk of visual loss by some 50% [ETDRSRG 85]. The unit of measurement was a loss of 15 or more letters (≥3 lines) on a logarithmic eye chart with 14 lines. This investigation demonstrates incontestably, that focal photocoagulation reduces the likelihood of vision loss from ME significantly. It also reveals, that panretinal, or scatter, photocoagulation is ineffective in treating ME.

The DRSRG study points to the same direction [Ferris 87]. Panretinal photocoagulation amplifies the risk of vision loss caused by ME. Eyes with both exudative DR and PDR should receive a combination of focal and mild panretinal treatment, the latter preferably spread out over several sessions. According to clinical findings in the Netherlands, focal photocoagulation may be quite effective, if the edema can be located distinctly. However, it is far less likely to treat a diffuse edema successfully [Hendrikse 85; Oosterhuis 84]. Diffuse ME is due to the widespread dilation of the capillary bed with the subsequent massive breakdown of the inner blood retinal barrier [Bresnick 86; L'Esperance 90:676]. According to an American investigation of 302 eyes with diffuse ME (no control group), a modified grid treatment had the following effect three years later. In 14.5% of the eyes visual acuity improved, in 60.9% it remained constant and in 24.6% it declined [Lee 91].

The grid technique closely resembles the scatter treatment of PDR, as both techniques have in common that radiation is spread over a certain area. A set of small coagula is created in the paramacular zone with distances between them of 100µ to 200µ. This

treatment uses a rather low to moderate energy intensity [Bresnick 86; Olk 86; Polak 89]. A comparison of five randomised studies of the effectiveness of photocoagulation in eyes with ME demonstrates, that this treatment significantly slows down vision loss caused by ME [Bresnick 86]. Recent publications on the ETDRS investigation endorse these findings [ETDRSRG 91a, 91b]. Over a period of five years after the start of the treatment, focal photocoagulation diminishes the risk of vision loss caused by exudative ME significantly. Therefore, it is no longer justifiable to deny photocoagulation to patients with exudative ME or to give them panretinal treatment only.

However, these results leave some questions without answer. The structure of the ETDRS raises some doubt, because nearly half the patients with ME seem to suffer from severe pre-PDR or mild PDR. Besides the option *"deferral of photocoagulation"* for the control group, the investigation contains four different treatment paths. At the very beginning of each path there is a panretinal treatment, with high or moderate intensity. Therefore, this investigation cannot provide evidence on the effectiveness of immediate focal photocoagulation followed by deferred panretinal radiation. Moreover, the publication seems to present contradictory statements on the optimal time of treatment. The following phrases illustrate this: (1) is hardly in harmony with (2) and (3).

(1) There was no suggestion that the timing of focal photocoagulation in the eyes with macular edema assigned to early photocoagulation influenced the development of severe visual loss. [ETDRSRG 91b:782]

(2) For eyes with macular edema and less severe retinopathy, each of the strategies of early photocoagulation had a reduced 5-year risk of severe visual loss compared with eyes assigned to deferral of photocoagulation ..., but the risks were low in all groups. ... Immediate focal photocoagulation with delayed scatter ... was the most effective strategy for reducing the risk of moderate visual loss for eyes with macular edema and less severe retinopathy. [ETDRSRG 91b:782-3]

(3) Deferral of photocoagulation in eyes with macular edema and more severe retinopathy was the least effective strategy. It was associated with the highest risk of both moderate and severe visual loss, although these differences were not statistically significant at the 0.01 level. [ETDRSRG 91b:783]

These studies provide clear evidence, that focal photocoagulation can only slow down the pace of vision loss in eyes with exudative ME. Only exceptionally this technique can stabilise central acuity, unlike the panretinal treatment of PDR.

After this brief review of pancreas transplantation and photocoagulation, *trans pars plana vitrectomy (TPPV)* should be mentioned for the sake of completeness. This operation usually involves the surgical manipulation of the vitreoretinal surface relationships and the removal of blood and fibrin from the vitreous cavity. It offers the last chance for eyes, where photocoagulation cannot control PDR [Hendrikse 89]. Several publications present evidence supporting the view, that TPPV is effective in stopping visual loss, when PDR reaches graver phases [Aaberg 81; Machemer 81; DRVSRG 85, 88]. This technique specifically suits the treatment of retinal detachment and persistent vitreous haemorrhages. TPPV is quite important for IDDM-patients, as they have to face PDR far more frequently than ME (cf. part C). The opposite is valid for NIDDM-patients (cf. part D). Moreover, PDR usually develops at a younger age, so that the disorder gets ample time to reach severe stages. TPPV has now being practised for over twenty years. Nevertheless, only a limited number of ophthalmologists perform this operation. The technique *de facto* profits a comparatively confined group of patients.

Consequently, in the near future only the second of the three treatment techniques specified above - (1) pancreas-transplantation, (2) photocoagulation and (3) TPPV - can be provided to a large number of diabetic patients. For this reason, the simulation considers photocoagulation as the exclusive means of tertiary prevention: panretinal photocoagulation for PDR, focal treatment for exudative ME and grid treatment for diffuse ME. This choice is mainly based on the above mentioned research results of the DRSRG [81] and the ETDRSRG [85, 91b]. The same studies are the point of reference to determine the success chances of these treatments. In case of PDR, success is defined as the stabilisation of the peripheral retina and peripheral vision. In case of ME, success is the reduction by one half of the deterioration speed of the macula and central acuity. These matters will be discussed more in depth later on (cf. section 8.8), alongside the starting points of the simulation.

3.7 Incidence and Prevalence

Several well-known publications present dissimilar results on these issues. What are the main causes of disagreement? First, there are diverse definitions of BR, ME, pre-PDR and PDR. Furthermore, ophthalmologists use various diagnostic techniques: ophthalmoscopy; fundus photography with or without mydriasis, with Polaroid film, black and white film plus green filter or colour slides and at different angles (e.g. 30° or 45°); stereoscopic colour fundus photography of seven standard fields; fluorescein-angiography. Some authors consider ophthalmoscopy as the *"gold standard"*, although

other investigations show, that this diagnostic technique is not perfectly sensitive and specific, even in ophthalmic departments [Sussman 82; Dasbach 91]. Additionally, the examined groups differ in size, age composition, average duration of DM, ethnic composition, social-economic stratification and the extent to which DM has been diagnosed. The duration of investigations also varies. Finally, these studies use different methods to pursue different goals. The majority are retrospective, while only some are prospective. Most investigations try to measure the prevalence, only some the incidence.

Apart from that, the notions *"retrospective"* and *"prospective"* have different meanings. In accordance with common parlance, these concepts relate to the starting point of an investigation. Facts regarding earlier moments are retrospective, whereas events that occur later are prospective. From another perspective, these two concepts are differentiated according to the relation between cause and effect. Retrospective studies investigate causes of effects that are already manifest. In case-control studies for instance, the outcome of exposure to a risk factor is apparent, when the investigation starts. The disorder is manifest in the group of cases, but it is not in the group of controls. According to this view, cohort studies are always prospective, because the effects of exposure to some risk factor appear, after the observation of the cohort starts [MacMahon 70:44]. The previous section uses the first - everyday - meaning of the notions *"retrospective"* and *"prospective"*.

The search for evidence on the incidence of DR requires circumspection. Some studies, like an investigation by Dwyer and associates [85], present data on the *cumulative incidence* of DR. This concept refers to the proportion of diabetic patients in a group initially without DR who develop DR during a certain period of time. Let us presume, that some investigation reveals the cumulative incidence R(0, j) from the beginning of year 0 until the beginning of year j $\{j \in \mathbb{Z}^+\}$. Then, the following relation exists between the incidence of DR among diabetic patients, ID, and R(0, j) [Kleinbaum 82:108 (modified)].

$$R(0, j) = 1 - e^{-\int_0^j ID(t)dt} \tag{3.1}$$

After deducing expression 3.2 from expression 3.1, the average yearly incidence $\overline{ID}$ (0, j) during the period of observation can be determined from R(0, j).

$$\overline{ID}(0,j) = -\frac{Ln[1-R(0,j)]}{j} \tag{3.2}$$

However, expression 3.2 can specify the yearly incidence in the period of observation with additional data only. This formula has another limitation. R(0, j) does not reveal how the group of diabetic patients is composed regarding risk factors such as age, sex, duration of DM, etcetera. This also requires additional information. The investigations by Klein and associates are the most widely known studies on the incidence of DM, not the least because they are remarkably consistent. Table 3.1 presents some key results of these studies. Apart from that, the first objection raised in connection with expression 3.2 also relates to these data.

	N	c	d	e	f	g	h	i	j	k
IDDM	996	28.3	13.8	59.0%	10.5%	41.2%	6.9%	8.4%*	1.5%	5.9%
NIDDM-a	674	63.1	14.5	47.4%	7.4%	34.0%	7.9%	8.4%&	3.2%	12.1%
NIDDM-b	696	66.0	8.1	34.4%	2.3%	24.9%	19.8%	2.9%#	2.7%	7.3%

a Insulin taking
b Not-insulin taking
N Number of patients
c Average age (years)
d Average duration of DM (years)
e No DR → DR
f No PDR → PDR
g Progression
h Regression
i No ME → ME
j Not blind → blind
k Doubling of visual angle

* N = 610
& N = 273
# N = 379

Table 3.1 - Four-year incidence and progression of DR, visual loss and blindness [Moss 88; Klein 89a, 89c, 89d]

Some numbers in table 3.1 require an explanatory note. Column N indicates the number of observed patients spread over three types of DM. These numbers apply to all columns, excluding column i. Besides data on the age composition and the duration of DM (columns c and d), table 3.1 presents percentages on the onset of DR. Thus, column e indicates, that 59.0% of all IDDM patients develop DR within the four-year period of observation. Among IDDM patients without PDR 10.5% have to face PDR within the same period (column f). Progression of existing DR occurs in 41.2% of the patients, regression in 6.9% (columns g and h). Finally, the columns i, j and k indicate the fraction of the patients who develop ME, become blind or experience the doubling to the visual angle. Mutatis mutandis, the same explanation applies to the next two lines of this table.

These investigations also disclose, that the likelihood of PDR among IDDM patients is virtually zero until the age of 13 years. Later, the probability gradually increases and reaches a maximum of 14% to 17% around the age of 30 years. These percentages indicate the incidence over a period of four years. After that age, the risk rate steadily falls to nearly 4%. Evidence on NIDDM patients reveals, that the threat of DR is also quite substantial in this group. As compared to IDDM, ME occurs far more frequently than PDR among NIDDM patients. Furthermore, a relatively larger number of NIDDM patients suffer from substantial visual loss, or even blindness. These results present a sharp warning. Until recently, NIDDM was quite frequently considered as a rather harmless variety of DM. The previous findings contradict this view, particularly regarding insulin taking NIDDM patients. Moreover, complications develop earlier after the diagnosed onset of NIDDM, as compared to IDDM. Recent studies by Klein and associates, on the contrary, throw doubt upon this relationship [91b, 92a, 92b].

Substantially more evidence is available on the prevalence of DR. The investigations by Klein and associates are also prominent in this respect, as a large number of references confirm. Table 3.2 presents some key data from these studies.

	IDDM		NIDDM-a		NIDDM-b	
	After 15 yrs	Maximum	After 15 yr	Maximum	After 15 yr	Maximum
DR	98%	98%	85%	95% §	58%	72% §
ME	15% §	33% §	29% §	38% §	13% §	28% §
PDR	25%	67%	15%	32% §	4%	15% §
Blind	3%	12%	3% §*	6% §*	3% §*	6% §*
§ graph reading * no separate data for NIDDM-a and NIDDM-b						

Table 3.2 - Prevalence of DR, ME, PDR and blindness (based on duration of DM) [Klein 84b, 84c, 84e, 84f; Moss 88]

A recent study of the prevalence of complications among IDDM patients in Pittsburgh, Pennsylvania, broadly confirms the percentages that table 3.2 presents on IDDM [Orchard 90a]. Another investigation of IDDM in Massachusetts reveals a lower prevalence of PDR after 15 years of DM, namely some 10% [Krolewski 86]. The prevalence reaches a maximum of roughly 70% among patients who develop DM before the age of 12 years and of over 50%, if the onset of DM is situated between the ages of twelve and twenty years.

A study in Rochester, Minnesota, discloses lower prevalence rates [Dwyer 85]. After 20 years of DM, almost 70% of the 75 examined IDDM patients suffer from DR and 20% from PDR. Furthermore, this investigation follows 1,031 NIDDM patients. The

prevalence of DR is 30.0 to 35.9% and of PDR 2.0 to 3.8%, where the higher percentages refer to obese persons. By contrast, this study unfolds a rather high prevalence of blindness, namely 20.0% unilaterally and 8.2% bilaterally after 20 years of DM among all observed patients. As mentioned earlier, the vast majority suffer from NIDDM.

A study of late complications among NIDDM patients in Heerde, the Netherlands, discloses, that the prevalence of DR and PDR equals 35% and 4% respectively [Verhoeven 90]. In 137 observed patients - besides a control group of 128 - DM was diagnosed on average 7.5 years earlier. Ten Doesschate presents data on the prevalence of blindness in the Netherlands [82]. DR is one of the three most important causes of blindness. Furthermore, it is striking, that DR provokes blindness mainly between the ages of 45 to 65 years. At earlier or later ages, blindness is most often due to other causes. These findings harmonise with the comparatively low prevalence of PDR among younger IDDM patients and with the reduction of life expectation as a result of DM.

What do these data mean for this investigation? First, they emphasise the lack of exact information on the prevalence of DR, and even more so on the incidence of DR. It is for instance virtually impossible to specify the incidence of DR, ME, PDR and blindness according to the age of patients or the duration of DM. Considerably more information exists on the prevalence, although it is quite divergent. However, in this context it is crucial, that these epidemiologic findings not only reveal differences but also important similarities. Nearly all investigations, for instance, point to a very high prevalence of DR among all diabetic patients after they suffer from DM for 15 years or more.

Furthermore, there is at least broad consensus on the prevalence of ME, PDR and blindness caused by DR. Surprisingly enough, after the onset of DM the relative spread of all these disorders roughly follows an S-shaped curve. Initially, the prevalence is unimportant, then it rises rather quickly within a limited number of years and finally it slowly approaches a ceiling value. If this simulation is to steer a prudent course, it might choose prevalence rather than incidence rates as starting points. Other simulations, however, are based upon incidence data. What is the rationale of this choice? And does a different choice make a fundamentally different approach necessary? The next chapter explores these questions.

4

Is a New Simulation Required?

4.1 Introduction

According to the prognosis presented in chapter two, the number of diabetic patients in the Netherlands may increase by some 22% to 40% towards the year 2005. The prevalence of DR will rise in the same proportion after a time lag of several years. Consequently, in the near future a substantially larger number of inhabitants may experience vision loss and blindness as a result of DR. It is still impossible to reduce the incidence of DM and DR significantly or to cure these disorders. Fortunately, modern ophthalmology offers laser treatment. It can shield most of these patients from blindness for a considerable number of years. As compared to operations on the retina, laser treatments are relatively inexpensive and hardly imposing upon patients. However, their effectiveness depends on reliable and up to date information about the condition of the retina. Eye examinations in quite a confined group of patients can provide this information at relatively low cost. What is the most effective strategy? And what personal, material and financial resources does it demand?

These questions do not apply only to the Netherlands: other western countries face similar problems. They also have an ageing population which consumes steadily increasing amounts of fat, while social and environmental factors make the onset of DM, and consequent DR, more likely. Some recent publications treat these questions with respect to the United States. They present results of computer simulations, that examine the cost-effectiveness of various scenarios of eye care. As it is hardly effective to invent the wheel again, so it seems worthwhile to investigate, whether one of these simulations suits the analysis of the situation in the Netherlands. Then, the structure of the model could remain unaltered and it would be sufficient to use different parameter values that bring the simulation in line with epidemiologic findings for the Netherlands. This is the starting point of the following *aperçu* of some recent publications.

4.2 Markov Processes and Monte Carlo Simulations

The publications at issue rest on Markov processes, with or without the Monte Carlo technique. This paragraph introduces some elements of these processes, illustrated with a simple example. It relates to a group of patients born in the same year. At the age of twelve, IDDM is diagnosed in all patients. The simulation follows all the patients individually from this diagnosis until death. It distinguishes three health states: *noDR, DR, Deceased.* At the age of twelve, no patient suffers from DR.

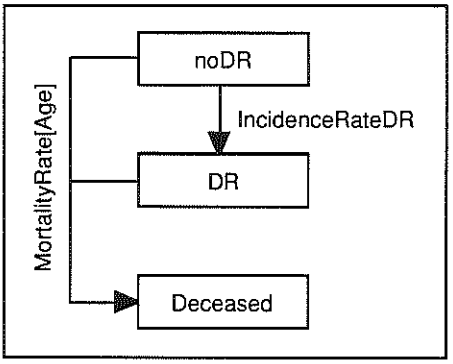

Figure 4.1 - Outline of a simple simulation

The arrows in figure 4.1 indicate, how a patient may traverse the scheme. This example allows only two routes. The first leads directly from *noDR* to *Deceased,* the second has *DR* as interim phase. It is impossible to return from *DR* to *noDR*. The transition probabilities are indicated next to the arrows: *MortalityRate[Age]* and *IncidenceRateDR*. These chances determine how many patients move yearly from one state to another. In this example, the hazard rate[1] merely depends on the age and the incidence risk of DR is constant. This discrete simulation partitions the time in periods of exactly one year.

Table 4.1 presents the development in a cohort, that initially holds 1,000,000 patients. The hazard rate equals 2% at each age, while the yearly incidence of DR is 5%. In the first year, 20,000 patients die and 49,000 patients develop DR ($= 0.05 \times 980{,}000$).

1 The discrete hazard rate $\lambda(g)$ at age g equals the likelihood of dying at age g after reaching age g. If T represents the age of death, the following formula represents this definition $\{g, T \in \mathbb{N}\}$ [Kalbfleisch 80:8].

$$\lambda(g) = P(T = g \mid T \geq g)$$

Thus, 931,000 patients are without DR. In the second year, the number of deaths equals 19,600 (= 0.02 × 980,000): 18,620 among patients without DR plus 980 in the group with DR. Among the remaining 912,380 patients without DR 5%, or 45,619, develop DR. Therefore, 866,761 (= 931,000 − 18,620 − 45,619) of the patients live at the beginning of the third year without DR. The number of patients with DR then equals 93,639 (= 49,000 − 980 + 45,619). The calculations for the remaining years follow the same lines. This explanation demonstrates, that the computation of each period applies the hazard rate before the incidence rate.

Age	noDR	DR	Deceased
12	1,000,000	0	0
13	931,000	49,000	20,000
14	866,761	93,639	39,600
15	806,954	134,238	58,808
16	751,275	171,094	77,632

Table 4.1 - Cohort development from 12 to 16 years (integer values)

In one specific period, a patient can find himself in one state only. The three states consequently constitute discrete states. Among other factors, preceding events determine the likelihood of being in a particular state in a particular period. For this reason, Markov processes unquestionably differ from procedures generating random numbers, that will be discussed later on. In the latter procedures, the probability of an event does not depend on previous events, as playing dice illustrates. That is to say, the result of perfectly casting a perfect die is unrelated to previous results.

The set of symbols 4.1 represents the likelihood of being in state i during period t, after traversing the states ... c, b, a during the periods ... (t − 3), (t − 2), (t − 1) in a history-dependent process with s different discrete states.

$$P[S_i(t) \mid S_a(t-1)\, S_b(t-2)\, S_c(t-3) \ldots] \tag{4.1}$$

$$\{1 \le a, b, c, \ldots i, \ldots r \le s;\ t \ge 1;\ a, b, c, \ldots i, \ldots r, s, t \in \mathbf{Z}^+\}$$

In this example the likelihood at issue depends exclusively on the state in the previous period. Formula 4.2 expresses this relationship.

$$P[S_i(t) \mid S_a(t-1)\, S_b(t-2)\, S_c(t-3) \ldots] = P[S_i(t) \mid S_a(t-1)] \tag{4.2}$$

$$\forall\ a, b, c, \ldots i, \ldots r, s, t$$

Moreover, the transition probabilities remain constant over time, as formula 4.3 indicates.

$$p_{ij} = P[S_j(t) \mid S_i(t-1)] \tag{4.3}$$

$$1 \leq i, j \leq s;\ p_{ij} \text{ independent of } t$$

This example reflects a Markov process. The cohort development can be computed with matrices. In each period, there is (1) a vector **a** typifying the distribution of patients over different states during the foregoing period, (2) a matrix **P** with transition probabilities and (3) a vector **b** representing the distribution of patients in the current period. The following relationship exists between **a**, **P** and **b**.

$$\mathbf{a} \times \mathbf{P} = \mathbf{b} \tag{4.4}$$

Formula 4.5 represents **a**, **P** and **b** symbolically as to this example.

$$[a_1\ a_2\ a_3]\begin{bmatrix} p_{11} & p_{12} & p_{13} \\ p_{21} & p_{22} & p_{23} \\ p_{31} & p_{32} & p_{33} \end{bmatrix} = [b_1\ b_2\ b_3] \tag{4.5}$$

$$\begin{bmatrix} 866{,}761 & 93{,}639 & 39{,}600 \end{bmatrix}\begin{bmatrix} 0.931 & 0.049 & 0.02 \\ 0 & 0.98 & 0.02 \\ 0 & 0 & 1 \end{bmatrix} = \begin{bmatrix} 806{,}954 & 134{,}238 & 58{,}808 \end{bmatrix} \tag{4.6}$$

Expression 4.6 presents the calculation, when patients reach the age of 15 years. Vector **a** indicates the cohort distribution over the three states at the age of 14 years. All elements in the lower triangle of matrix **P**, below the diagonal, equal zero, or $p_{ij} = 0$ for $i > j$. In other words, patients cannot return to a state that they left earlier. Element p_{13} indicates the yearly death rate of patients without DR (2%). Among the remaining 98% five per cent develop DR, which is equal to 4.9% of the patients not suffering from DR at the age of 14 years, or $p_{12} = 0.049$. Element p_{11} ($0.931 = 1 - 0.049 - 0.02$) represents the likelihood of the *status quo ante* (1 – the total probability of change). For similar reasons p_{22} equals 0.98. Because death is a fully absorbing state, element p_{33} equals 1. In other words, the states *noDR* and *DR* are so-called *transient*, or temporary, states. After leaving a *transient* state, it is impossible to return to that state [Kemeny 76:35]. The state *Deceased* is absorbing, as patients remain indefinitely in that state, after they die.

This fast and accurate calculation method offers the opportunity to determine the variance of results, to perform sensitivity tests and to assess expected utilities in the framework of cost-utility analyses [Beck 83]. However, this technique also has some substantial drawbacks.

As a rule, fixed transition probabilities are only justifiable in the short run. But in the longer run, the simulation should accommodate to age-dependent hazard rates and fluctuating incidence ratios. This is feasible by allowing the elements of matrix **P** to fluctuate as time goes on. However, these changes prohibit to establish the variance of the results. This method also excludes following patients individually. The most substantial drawback, however, relates to determining the values of the elements in matrix **P**. The number of elements grows exponentially, if the simulation distinguishes more states. In case of s states, there are s^2 transition probabilities. Moreover, the calculation of transition probabilities involves some complications that are merely attributable to this technique. This obstructs the refinement of these simulations. Element p_{12} illustrates such a complication. As indicated earlier, this element does not equal the incidence rate of DR, but the product of the survival chance and the incidence rate. As the number of elements in matrix **P** increases, these complications become considerably more substantial.

The Monte Carlo technique bypasses such complications. It uses random numbers. They may be drawn from any distribution, but most simulations choose numbers from a uniform distribution. It is possible to transform these numbers into numbers drawn from other distributions, like the standard normal distribution [Putten 79]. With the Monte Carlo technique, a simulation might imitate the evolution in a cohort of diabetic patients starting from the data mentioned earlier in this paragraph. Numbers are drawn from a uniform distribution covering the interval [0,1). Consequently, each real number x $\{0 \leq x < 1\}$ has the same probability of being selected. At the beginning of each period, a random number x is drawn for every living member of the cohort. Is x smaller than the hazard rate, then the patient dies. Otherwise, a second random number x is drawn, provided the patient does not suffer from DR. The patient develops DR, if the second random number is smaller than the incidence rate of DR. The Monte Carlo technique enables simulations to follow patients individually. In this process, random numbers not only determine which route each patient takes in the simulation scheme (cf. figure 4.1), but also the length of stay in every state. The incidence of DR is determined directly on the basis of the incidence rate. The complication mentioned earlier regarding element p_{12} of matrix **P** fails to eventuate.

The following fragment of a computer programme - written in Pascal - illustrates how to implement this technique. The programme uses the array *Patient*, that contains one element for each patient. At any moment, every element represents one of the three states to indicate the situation of the patient in question. The value *noDR* is assigned to all elements of the array *Patient*, when the simulation starts.

```
 1.  for N := 1 to NumberOfPatients do begin
 2.     Age := 12;
 3.     while not (Patient[N] = Deceased) do begin
 4.        if Random < MortalityRate[Age] then
 5.           Patient[N] := Deceased;
 6.        if Patient[N] = noDR then
 7.           if Random < IncidenceRateDR then
 8.              Patient[N] := DR;
 9.        Age := Age + 1
10.     end
11.  end;
```

The above instructions are the nucleus of the simulation. Line 1 opens an iterative loop ending on line 11. All integers from 1 to the integer number stored in the variable *NumberOfPatients* are consecutively assigned to the variable *N*. After the variable *Age* receives the initial value 12 on line 2, line 3 opens a conditional iterative loop ending on line 10. The condition on line 3 contains the variable *Patient[N]*, that represents the state of patient *N*. While patient *N* is alive, the computer executes the instructions on the lines 4 to 9 iteratively. The function *Random*, activated on line 4 and line 7, generates a random number drawn from the uniform distribution covering the interval [0,1).

The instruction on line 4 relates the hazard rate to the age of patient *N* by choosing a particular element from the array *MortalityRate*. A further differentiation of hazard rates is quite feasible, for instance by gender and health condition. If the random number is smaller than the hazard rate, element *N* in the array *Patient* receives the value *Deceased* on line 5 and patient *N* passes away. Consequently, the condition on line 6 is false and the instructions on line 7 and 8 are not executed. After increasing the age by one year on line 9, programme execution recommences on line 3. The computer there discovers that the condition is false and halts the execution of the conditional loop, embodying the lines 3 to 10.

Line 1 is then executed again and the value of variable *N* increases by one. If not all patients have been processed yet, the variable *Age* once more receives the start value 12 and the computer executes the conditional iterative loop, until this patient dies. While the random number on line 4 is not smaller than the hazard rate, the computer skips line 5. If the patient does not suffer from DR, the condition on line 6 is true. Line 7 then instructs the computer to compare a random number with the incidence rate of DR. For convenience' sake, the simulation uses a fixed value for this rate, stored in the variable *IncidenceRateDR*. Is the random number smaller than this rate, then element *N* in array *Patient* is assigned the value *DR* and patient *N* develops DR. Figure 4.2 presents the routes a living patient may follow in one period.

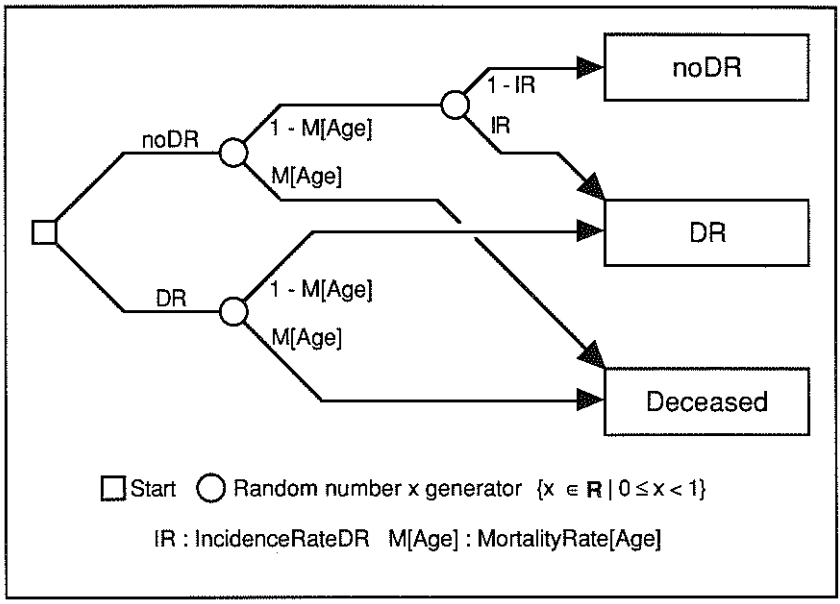

Figure 4.2 - Schematic representation of routes in the computer simulation

This programme fragment gives scope for critical notes on the Monte Carlo method. After the earlier comment in this section on transition matrix **P**, it is self-evident to examine the lines 4 to 8. They consist of instructions that govern the transition from one state to another. These instructions are surprisingly simple. Moreover, they can easily be adapted to a further differentiation of hazard and incidence rates. Hazard rates might, for instance, be distinguished according to gender by giving the array *MortalityRate* a second dimension to accommodate separate rates for females and males. Then, an extra parameter *Sex* should be added to *MortalityRate* on line 4. Hazard rates from demographic tables can directly be inserted into the array *MortalityRate*.

It is quite feasible to differentiate the incidence rate. For that purpose, the variable *IncidenceRateDR* should be replaced with an array of one or more dimensions, depending on the nuances of the available evidence. Epidemiologic data may be assigned to this array directly, without modifications like the one discussed earlier in this section regarding element p_{12} of matrix **P**. Besides some minor programme alterations, it suffices to add a few parameters to the instruction on line 7. This supports the view, that the Monte Carlo technique may present fewer obstacles than the matrix method, when a simulation requires refinement. Part B of this manuscript presents a simulation, that confirms this statement.

Furthermore, the Monte Carlo technique offers at any time personal information on any member of the cohort. It can generate data sets that are large enough to determine means and deviations with little doubt. Moreover, the diversity of individual results creates favourable test conditions. This technique automatically produces dissimilar situations, that try the quality of the programme in combination with varying values of variables. If these data sets were not available, programmers might conceive critical settings to test programmes. However, they may easily overlook some critical situations, even in rather straightforward simulations.

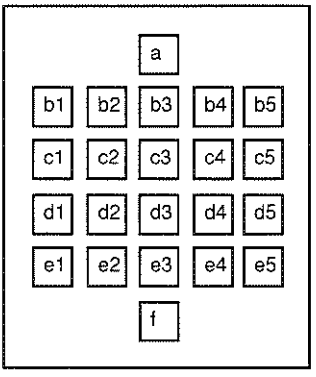

Figure 4.3 - Scheme of a modular simulation

Empirical tests of computer programmes have fundamental limitations. Figure 4.3 illustrates some of them. The diagram refers to a simulation that must be traversed in six successive steps: a, b, c, ... f. Each step b, c, d or e has five variations. Any variation of any step may succeed any variation of the previous step. Consequently, the number of conceivable paths equals 5^4, or 625. The successful passing of all these paths does not provide, however, an absolute proof of programme correctness. Usually, a programme uses some variables that may accept a wide range of values. An empirical test is only complete after the examination of all possible combinations. There is however

no algorithm that generates an adequate set of test data for an arbitrary program [Goldschlager 88:100].

Obviously, the Monte Carlo technique has drawbacks. The reliability of the results also depends on the cohort size. However, there are no generally accepted guidelines for the minimal cohort size. Some authors recommend including at least 1,000 or 10,000 patients [Beck 83; Dasbach 91]. In case of complex simulations, such cohorts require several hours, or even days, of computer processing. This handicap is becoming less important, as hardware prices fall.

The main, or random access, memory of smaller computers is on average much larger than a few years ago. It can now hold the complete data set of larger cohorts. In the past, processing required secondary memory elements, like disks, for the intermediary storage of such data sets. The expansion of main memories permits startling increases in processing speeds, because the access to main memory is 1,000 to 10,000 times faster than to secondary memory. For that reason, the capacity of the main memory in smaller computers used to be a serious obstruction to simulate larger cohorts. Nevertheless, the processing of several alternatives, that is to say performing a what-if analysis, can be time consuming even with modern equipment. Despite these limitations, the Monte Carlo method in combination with a Markov process is quite frequently the obvious technique for simulations. The next simulation on DR emphasises this. Thereafter, a second simulation will be presented that uses a Markov process only.

4.3 The Simulation by Javitt and Associates

Several variants of this simulation exist [Javitt 88, 89, 90, 91]. This section discusses the 1991 version. It analyses the cost-effectiveness of eye care for IDDM patients from the perspective of a governmental agency that evaluates the costs and savings at American prices in 1990. The simulation includes 17,245 patients. This number, as well as the initial age composition of the cohort, reflects the estimated yearly incidence of IDDM in the United States. The simulation follows each individual separately from the onset of IDDM until death. The time interval between these two events consists of periods lasting two months. In each period, each patient can face only one health state. Random numbers, drawn from a uniform distribution covering the interval [0,1), determine the disease progression, the compliance with guidelines for ophthalmic care, the outcome of diagnoses, the effectiveness of treatments and the moment of death.

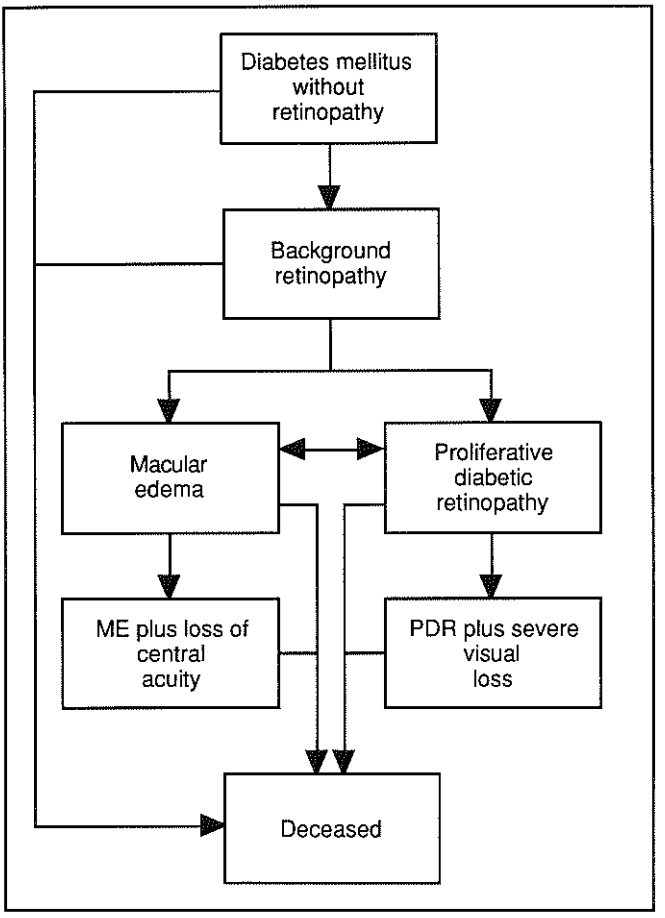

Figure 4.4 - Scheme of the simulation by Javitt and associates

The simulation uses (1) official demographic data for the United States plus (2) results of cross-sectional studies and clinical trials on IDDM, DR and the effectiveness of photocoagulation. The chapters two and three of this manuscript present appropriate bibliographic references. At the start of the simulation, no diabetic patient suffers from DR. In each period, the programme first activates the mortality module. It draws a random number x {$0 \leq x < 1$; uniformly distributed} for each survivor. A patient dies, if the random number is smaller than the individual hazard rate, that depends on gender, age and health state. In case the patient survives, the epidemiologic module generates a second random number and determines the disease progression by comparing this number to the incidence rate of the next disease phase. Figure 4.4 presents the various stages schematically. This simulation uses a limited set of values for incidence rates. The annual likelihood of *Background retinopathy*, for instance, equals 5.0%

during the first four years after the onset of IDDM and 20.0% in later years. With these two percentages the simulation aims at approximating epidemiologic evidence.

Previous versions of this simulation presume, that all patients fully comply with the guidelines for ophthalmic care. A recent study in the state Wisconsin reveals however, that nearly half the IDDM patients do not follow the currently suggested eye care schemes [Dasbach 91]. For that reason, the 1991 version of this simulation uses random numbers that determine to what extent patients comply with guidelines for ophthalmic care. The results of eye examinations partly depend on random numbers as well. This reflects the empirical finding that ophthalmoscopy is less than 100% sensitive and specific [Sussman 82]. As a result of diagnostic errors, a patient may therefore receive laser treatment erroneously or be excluded from photocoagulation wrongly. The simulation derives screening and treatment costs from U.S. Medicare charges in 1990. The cost of blindness includes U.S. social security payments, tax expenditures, tax losses and federal payments to Medicare and Medicaid.

The simulation discloses savings of more than 47,000 years-sight (mean: 2.75 years), if 60% of the patients receive eye care according to the preferred practice pattern of the *American Academy of Ophthalmology*: dilated ophthalmoscopy every six months for patients with DR and annually for patients with no DR. The remaining 40% receive no eye care. In case all patients comply with this pattern, the savings rise to over 79,000 years-sight (mean: 4.59 years). The estimated savings of U.S. federal budgetary costs range from over $100 million in the first scenario to nearly $170 million in the second. These amounts are the credit balance of the following mutations: (+) volume reductions of social security insurance claims and social disability insurance claims, (+) higher tax receipts and (–) extra Medicare and Medicaid expenses.

This brief review evokes comment. The simulation uses a small set of fixed incidence rates and approximates the disease progression stepwise with a few health states. This contrasts with the nearly continuous, that does not mean constant, actual development of DR. The Markov process, forming the pivot of this simulation, offers no other choice, though. It has a finite number of discrete states - specified in figure 4.4 - plus a limited set of transition probabilities. Furthermore, data on the incidence of DR are sparse, as section 3.6 indicates. The available evidence relates to periods of some four years. Is this information valid for a simulation embracing more than 60 years?

The Markov process in this simulation invokes another limitation. As DR develops continuously or nearly continuously, the likelihood of prognostic errors is inversely related to the difference between the actual condition of the retina and the border value

of two disease conditions, like BR and PDR. For that reason, the sensitivity and specificity of ophthalmoscopy both have variable, rather than fixed, values. The number of discrete states in this simulation, however, prohibits establishing a functional relationship between the condition of the retina and the quality of eye examinations.

For similar reasons, it is also difficult to evaluate the effectiveness of photocoagulation. As the retina is exposed longer to a severe variant of DR, sight-threatening damage of the retina becomes more probable. Simultaneously, the chances of preserving vision by laser treatment deteriorate. The previously mentioned studies on the effectiveness of panretinal and focal treatments present average success rates [DRSRG 81; ETDRSRG 85]. However, average rates are inadequate in a simulation that aims at assessing effects of more intensive eye care. A higher screening frequency may reveal the need of photocoagulation earlier, when DR has had less time to damage the retina. Therefore, the overall success rate of photocoagulation is positively related to the frequency of eye examinations. However, the Markov process in this simulation distinguishes only a limited number of health states. It stores no information on past individual development (see: formula 4.2). For these reasons, this simulation cannot relate the success rate of laser treatment to the frequency of screening. This affects the reliability of results on vision gain.

The exclusion of regression is another limitation of this simulation. Without laser treatment, regression occurs in some 4% of the eyes with PDR [Hendrikse 90:11]. The cost-effectiveness is assessed with data for the United States. Even after adjustments, the results should be applied cautiously to the Netherlands. And finally, the simulation does not present separate results for males and females. Despite these shortcomings, the simulation by Javitt and associates represents a pioneering approach.

4.4 The Simulation by Dasbach and Associates

This simulation investigates the costs and benefits of eye care for three groups of diabetic patients: (a) IDDM, (b) NIDDM-a, (c) NIDDM-b [Dasbach 91]. It adopts the viewpoint of an imaginary state health agency that provides all funds for ophthalmic care, disability facilities and revalidation. The simulation recognises five health states: (1) low risk DR, (2a) treated high risk DR, (2b) untreated high risk DR, (3) blindness and (4) death. It does not analyse ME separately. Fixed transition probabilities exist between the states (1) to (3). They were taken from the Wisconsin *Epidemiologic Study of Diabetic Retinopathy (WESDR)* on the progression of DR observed at two intervals, four years apart [Klein 84a, 84b, 84c]. These findings were adjusted to

simulate the development of DR in the absence of ophthalmic care. For reasons of simplicity, the simulation excludes regression.

$$\lambda_{ags} = r_{gs} \times \lambda_a \tag{4.7}$$

Formula 4.7 indicates, that the age-adjusted hazard rates λ_{ags} equal the product of the risk factor r_{gs} and the age-adjusted hazard rates of the general population in the state Wisconsin λ_a. The risk factors have a fixed value ($r_{gs} \geq 1 \ \forall \ r_{gs}$) for each disease state s and for every patient group g. There is no distinction regarding gender.

The simulation analyses the disease progression with Markov processes and computes the cohort development with matrices. The transition matrix contains time independent elements for the transition between the states (1) to (3) plus time dependent elements on mortality. As regression is excluded, all elements p_{ij} equal zero for $i > j$ (see: formula 4.5, section 4.2). The simulation distinguishes three screening programmes.

C_1	direct ophthalmoscopy (mydriatic dilation)
C_2	nonmydriatic fundus photography (physiologic dilation)
C_3	seven-field stereoscopic fundus photography with colour slides (mydriatic dilation; considered as gold standard)

Table 4.2 - Three screening programmes (binocular)

For each of the three patient groups, the simulation examines seven scenarios.

S_1 :	no ophthalmic care	S_2 : once every 2 years C_1	S_5 : once a year C_1
		S_3 : once every 2 years C_2	S_6 : once a year C_2
		S_4 : once every 2 years C_3	S_7 : once a year C_3

Table 4.3 - Seven ophthalmic care scenarios

It simulates screening programmes lasting for 10 and for 60 years. The compliance with ophthalmic care in the scenarios S_2 to S_7 is based on evidence gathered in the WESDR over a period of five years. Table 4.4 summarises these findings.

Patient group	Never	Sometimes, at best once every 2 years	At least once a year
IDDM	22.0%	26.0%	52.0%
NIDDM-a	40.0%	16.0%	44.0%
NIDDM-b	40.0%	21.8%	38.2%

Table 4.4 - Compliance with eye care in the WESDR (related to each group total)

All results in table 4.5 refer to simulations covering 60 years and 1,000 patients. As compared to the scenario without ophthalmic care, S_7 generates the largest sight gain. This is hardly surprising, because S_7 offers the best screening method and the highest frequency. It is remarkable though, that ophthalmic care generates cost reductions among IDDM patients only. In both NIDDM groups, the sight gain does not yield enough financial savings to counterbalance the costs of eye examinations. The IDDM results may be contrasted with the estimates in the previous simulation. In case of comparable compliance, Javitt and associates forecast 2.75 years of sight gain per patient, Dasbach and associates 0.32 years.

Patient group	Scenario	Sight gain in years with regard to S_1	Increase of costs with regard to S_1
IDDM	S_7	318.8	– $ 1,021,069
NIDDM-a	S_7	62.3	+ $ 32,849
NIDDM-b	S_7	20.8	+ $ 137,350

Table 4.5 - Largest sight gain scenarios

What accounts for this dissimilarity? The simulation by Javitt and associates discounts sight gain at 0%. Consequently, discounting does not affect the present value of future benefits. Dasbach and associates, on the contrary, discount sight gain at 5%, which roughly halves the present value of benefits realised after 15 years[2]. The time distribu-

2 If the yearly sight gain is realised on average half-way across the year, the present value of the total sight gain C, at the start of the simulation, can be determined with the following formula.

$$C = \sum_{t=1}^{n} \frac{1}{(1+i)^{t-0.5}} Y_t$$

Y_t : sight years gained in year t

i : interestperunage per year

n : duration of the simulation in years

tion of sight gain in the latter simulation happens to disclose, that the frequency reaches its maximum some 15 years after the start of the simulation. Following adjustments for unequal discounting rates, Javitt et al. forecast over four times more sight gain than Dasbach et al. This discrepancy mainly results from diverging data on the progression of DR and from the analysis of ME, separately or otherwise. Because of the incongruity, the results of these simulations should be considered cautiously. This scepticism may be appropriate to any simulation of a similar nature. For scenarios with the largest sight gain, table 4.5 also reveals, that ophthalmic care enables cost reductions among younger onset patients only. For each patient group, there is however at least one scenario, that offers cost reductions. The savings for NIDDM are considerably smaller than for IDDM, though.

Patient group	Scenario	Sight gain in years with regard to S_1	Increase of costs with regard to S_1
IDDM	S_5	303.1	– $ 1,096,765
NIDDM-a	S_2	48.3	– $ 70,800
NIDDM-b	S_2	14.8	– $ 144

Table 4.6 - Lowest cost scenarios

After the presentation of results, it seems appropriate to evaluate the simulation by Dasbach et al. briefly. The inclusion of NIDDM and the distinction of several diagnostic techniques gives this simulation an extra dimension. Moreover, matrix calculations can assess alternative scenarios swiftly. This simulation also has shortcomings, though. Apart from mortality, the disease progression depends on fixed transition probabilities. These are hardly tenable in simulations that cover 60 years. The analysis excludes ME, although this is the most significant sight-threatening variant of DR among older onset patients. Moreover, Dasbach et al. distinguish fewer disease states than Javitt et al. As these states are discrete, the comment in the previous section also applies to this simulation.

(continued)

On the assumption that the total sight gain Y is concentrated at the end of the 15th year, C can be calculated with the next formula. C is nearly half Y, if the interest rate equals 5%.

$$C = \frac{1}{1.05^{15}} Y$$

4.5 The Need of a New Simulation

For several reasons, these two simulations encourage further research. First, this analytical method opens new horizons. The selection of control groups creates no ethical problems, even if the effectiveness of a treatment, like photocoagulation, is demonstrated irrefutably. This technique also enables swift and accurate inquiries into the relationship between a hypothesis and the disease progression in a larger group of patients. Figure 4.5 presents a general scheme, where assumptions besides parameters based on evidence make up the input. The model contains instructions that determine how to process the input. The results are part of the output of the process.

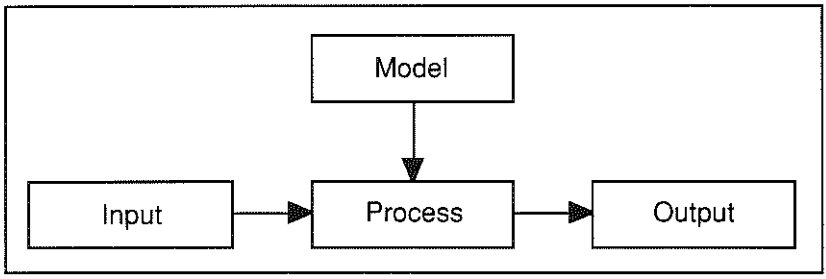

Figure 4.5 - General scheme of a simulation

Second, the limitations of the two simulations are also challenging. Through their flexibility, the simulation techniques make room for improvements that may generate new instruments to evaluate the cost-effectiveness of ophthalmic care for diabetic patients. As figure 4.5 illustrates, these alterations might involve both the input and the model. What are the most important changes, that the existing simulations require? The comment on the simulations by Javitt et al. and Dasbach et al. focuses on the contrast between the complex actual development of DR and the simulated disease progression through a limited number of states. The sparseness of epidemiologic evidence on DR and the limited number of well-known simulation techniques may explain the choice of this discrete approach.

A closer approximation of clinical developments requires techniques that allow a more gradual simulation of the disease progression. For that reason, the Markov process in the simulation may distinguish far more disease states. The set of transition probabilities will then grow exponentially. It is doubtful, whether epidemiologic evidence provides firm ground for this refinement. The simulation presented in part B offers a solution for this problem. With a limited set of data, it can generate an infinite number of values to characterise the condition of the retina. The simulation describes only a few

aspects of the retina, as it has to face general limitations of models. Therefore, a model will never fully correspond with the retina itself. The simulation follows the following aspects: (1) the macula, (2) the peripheral retina, (3) central acuity and (4) peripheral vision.

This simulation may also meet other requirements. It might accord with the process of observation, diagnosis and therapy in ophthalmic care for diabetic patients. This process has dissimilar paths like the branches of a decision tree. These paths concern (1) the variants of DR, (2) the sensitivity and specificity of screening techniques, (3) the different types of laser treatments and (4) the effectiveness of these treatments. The alternative simulation presented in part B should do more justice to these aspects than the simulations presented in previous sections. Normally, such simulations use incidence rates rather than prevalence rates. The latter reflect several movements that occur simultaneously, like changes of (1) the population composition, (2) the incidence rates, (3) the diagnostic criteria, (4) the compliance with eye care and (5) the effectiveness of diagnostic methods and treatments. In this *"turmoil"*, it seems barely reasonable to depart from prevalence rates.

Nevertheless, the alternative simulation resorts to prevalence rates, because the available incidence rates relate to a limited number of age categories and exclude ME [Klein 89a, 89c]. This restricts the reliability of simulations that cover all ages and different groups of diabetic patients. In the near future, more reliable incidence rates may become available. This evidence can be transformed into prevalence rates with standard demographic techniques that may account for changes in the population composition. After this transformation, the incidence rates can be included indirectly into the simulation. In short, the choice of prevalence rates offers at present more certainty, without excluding the use of incidence rates in the future. This is a compromise though, that may be a subject of discussion.

Furthermore, the simulation should distinguish between males and females, if only for differences in mortality. Like the simulation by Dasbach and associates, it must be capable of following several groups of diabetic patients. It also ought to offer facilities for *"what-if"* analyses to examine variations of the factors mentioned above, as well as the compliance, the treatment costs and the discount rate. These facilities enable the simulation to generate forecasts, not only for the Netherlands, but also for other countries. Finally, the simulation should have a general nature, that makes this technique useful for investigating the management of other complications as well.

The demarcation of this investigation prohibits the treatment of this matter in depth. However, it is worth mentioning, that the technique of the alternative simulation requires only a small set of epidemiologic data to generate a continuous, or nearly continuous, disease progression. Moreover, this technique is not confined to DR. It is able to analyse the evolution of any disorder with a severity that can be represented in the interval (0, 1), provided a small set of data is available on the distribution within the interval. Part B presents further details on this subject. Besides generally applicable components, the simulation also embraces components that relate specifically to DR, like the modules on ophthalmic screening and laser treatment. An investigation of other complications requires adjustments of these specific components.

Several arguments seem to justify the development of a new simulation. Before the presentation of this technique in part B, the next chapter presents the main research questions and an outline of this manuscript.

5

Research Questions and Economic Assessment

5.1 Research Questions

Modern ophthalmic techniques offer new perspectives to diabetic patients. Ophthalmologists need adequate data on the progression of DR to decide timely, whether laser treatments or operations are indicated. With this information, they may reach their maximum efficiency. The prompt implementation of these decisions postulates adequate ophthalmic resources. In case of lacking ophthalmic capacity, waiting lists are unavoidable though. Some patients are then temporarily exposed to uncertainty. Meanwhile, they may develop new complications that reduce the effectiveness of treatments. This brings up the central issue of this investigation.

> *How much blindness caused by retinopathy among diabetic patients can ophthalmic examinations and timely laser treatments prevent?*

This question relates to the effectiveness of ophthalmic care. Obviously, there are also financial repercussions. They raise three related questions.

> *What resources does this care require?*
>
> *What costs does it generate?*
>
> *What savings does it permit?*

5.2 Economic Assessment

The last three questions in the previous section refer to economic assessment. There are several methods for economic evaluation: (1) cost analysis; (2) cost-minimisation

analysis; (3) cost-effectiveness analysis; (4) cost-utility analysis and (5) cost-benefit analysis. To which method is this study affiliated? These five evaluation methods have similar guidelines for identifying costs. They use different criteria to delimit and to measure benefits. Broadly, these five methods have the following characteristics.

(1) *Cost analyses* do not consider benefits. (2) *Cost-minimisation analyses* compare techniques - some diagnostic methods, for instance, or some therapies - that yield equivalent outcome. For that reason, no measurement problems can emerge. (3) *Cost-effectiveness analyses* compare techniques with different outcomes that are measured in physical units, like life- or sight-years gained. This method has two important limitations. First, it uses incommensurable measurement units that prohibit comparing costs and benefits. Second, this method usually leads to in an incomplete or biased description of benefits. Studies of life-prolonging operations illustrate this point. Some of them stress the expected prolongation of life, while they pay little attention to the quality of life after the operation. However, both the quantity and the quality of the extra life-years determine the utility of a treatment. For that reason, an operation offering a rather long prolongation of life may have a smaller utility than an operation offering a smaller prolongation of life with a significantly higher quality. If patients have a choice, they will select the second alternative, provided health care insurers fully reimburse the costs of both operations. However, cost-effectiveness analyses do not offer enough information to determine utilities and to follow the preferences of patients.

(4) *Cost-utility analyses* aim at eliminating the second limitation by determining the expected utility of the alternatives under consideration. (5) *Cost-benefit analyses* bypass the first limitation by evaluating both costs and benefits in monetary units. Obviously, the last two evaluation methods are as such superior to cost-effectiveness analyses. Quite frequently, it is impossible however to determine the utility or the monetary value of health effects. One of the first three methods must then be accepted as an alternative [Drummond 80:6-19; Engleman 86; Guyatt 86; Blades 87; Drummond 87:27-8, 114].

Which methods does this study use? The last question in the previous section mentions savings, that may result indirectly from the preservation or the slower deterioration of vision. A decrease of visual impairment involves reductions of social security and disability payments. In other words, this investigation aims at expressing some benefits in monetary units. That would justify the name *cost-benefit analysis*. However, this study expresses the most important benefit, sight gain, in physical units, because there is no consensus yet on the translation of sight gain into monetary units or utilities

[Drummond 86, 88]. The next quotation from the conclusion of a recent literature study on visual impairment confirms this.

> *"This review has shown that while there has been some measurement and valuation of health states relating to visual impairment, this is so far limited. In particular, most clinical trials of interventions to reduce visual impairment restrict their measurement of success to traditional indicators such as visual acuity or visual field." [Ferguson 90:88-9]*

Although the present study may be situated somewhere between a pure cost-effectiveness analysis and a pure cost-benefit analysis, it is clear, that the former type of analysis is predominant. The title of this manuscript therefore contains the term cost-effectiveness analysis, not the least to avoid excessive expectations. This choice corresponds to the following statement by Friedman [72].

> *"..... I believe that we economists in recent years have done vast harm - to society at large and to our profession in particular - by claiming more than we can deliver."*

5.3 Outline

What are the principal components of the strategy to answer the questions presented in section 5.1? The previous chapters refer to two cornerstones: (1) epidemiologic data from reports in major medical publications and (2) the alternative simulation model. Part B reveals essential characteristics of this model from a methodological point of view. It presents a limited set of technical details. Besides, part B accounts for the presumptions.

The first chapter of part C justifies the input data and the parameters. Part C then presents the main simulation results regarding IDDM patients. It finally discusses these results. Part D has a similar outline as part C. It relates to NIDDM and distinguishes insulin taking and not-insulin taking patients.

The results in part C and part D are the basis of the prognosis presented in part E. It sets out the requirements of ophthalmic care for diabetic patients in the Netherlands until the year 2020. The forecast departs from three demographic scenarios by the *Central Bureau of Statistics (CBS)* for the Netherlands. The last chapter of part E offers a discussion.

The main conclusions of this investigation appear in part F. Part G summarises the previous parts in Dutch. The appendix presents the meaning of abbreviations, key concepts, bibliographic references and some technical details.

B

Methods

6

Legitimation

6.1 Introduction

The use of simulations postulates justification, because the methodology of medical research usually highlights other techniques, like experimental, case-control and cohort studies. For that reason, the sections 6.2 to 6.5 confront the research questions, presented in the previous chapter, with these *"classical"* methods. Section 6.5 then assesses what support simulations provide in analysing the research questions. Among these, only the central issue - the connection between ophthalmoscopy, laser treatment, and the reduction of visual impairment - has a pure medical nature. Once this relationship has been clarified, economic parameters virtually suffice to answer the related questions on resources, costs and savings. Hence, this chapter relates the various methods to the central research issue only.

6.2 Experimental Studies

In this context, these studies require splitting up diabetic populations at random into several groups. Each group receives a special scenario of ophthalmic care. With respect to all other relevant characteristics, the groups should be fully comparable. The control group receives no eye care. Patients in other groups have eye examinations at regular intervals, that are specific to each group. If an eye examination discloses that photocoagulation is indicated, the patient receives laser treatment shortly afterwards. Finally, the investigator assesses, whether the incidence or the prevalence of blindness and moderate vision differs significantly between the various groups.

This study design raises several questions. Is it sufficient to isolate the intensity of ophthalmic care? Or is a further differentiation required according to pathogenesis, treatment of DM, age of incidence and socio-economic status? How many patients

should the investigation include? Is it justifiable for the sake of feasibility to select a population with a relatively high incidence of DR? Is the control group truly comparable to the other groups? Is a double blind random splitting up of the population feasible? Which effect has non-double blind random assignment on the diagnosis and the compliance? Are withdrawn patients representative of the total population, or of the subgroup they belong to? How are findings of withdrawn patients processed? What procedures are followed, when significant evidence appears on the effectiveness of the treatment? Do all patients comply with the prescribed scenario of eye care? What is the optimal combination of duration and population size within the framework of certain financial constraints? When should the investigation end? Are the results published, after they come up to scientific standards? Or are concessions made to diabetic patients outside the study population who solicit being informed as early as possible? Is the study protocol adequately detailed to repeat the investigation in similar conditions and to test the results? [MacMahon 70:283-99; Peto 76, 77; Kleinbaum 82:42-4; Sturmans 84:245-74; Weiss 86:48-71; Armitage 87:172-9; Kleijnen 91]

Although this set of questions is not complete, it calls forth serious objections. They primarily relate to the minimally required duration of such studies. On account of the average number of years between the onset of DR, PDR, ME, moderate vision and blindness, a population of diabetic patients should be observed for at least five to ten years. It is doubtful however, whether this period would suffice to investigate the subject thoroughly. Besides, the time to prepare the investigation, process the data and publish the results should not be underestimated. Would it be a socially acceptable to postpone policy decisions meanwhile, even though the effectiveness of photocoagulation has been demonstrated unequivocally quite some years ago [DRSRG 81; ETDRSRG 85]? An affirmative answer to this question would probably arouse a storm of ethical objections. Moreover, the present volume of luxurious consumption in western countries provides few arguments for withholding ophthalmic care that can prevent a considerable amount of blindness and moderate vision with comparatively inexpensive treatments.

However, this type of investigation evokes ethical objections. The certitude on the effectiveness of photocoagulation makes it inadmissible to offer some patients limited ophthalmic care and to exclude others altogether, even in the framework of a test. Paradoxically, successful experimental studies create insurmountable barriers for further tests in the same sphere. Analysing the remaining questions in this section is therefore unnecessary.

6.3 Quasi Experimental Studies

Are quasi experimental studies a defensible alternative? By the absence of a control group some ethical objections disappear. However, these investigations offer few external controls. This may impair the reliability of the results. Besides, these investigations require at least as much time as experimental studies. Finally, it is hard to imagine how to analyse several scenarios simultaneously without ethical problems [Kleinbaum 82:44-7]. For these reasons, quasi experimental studies are not a justifiable choice.

6.4 Cohort Studies

These studies are observational. Consequently, they do not give rise to ethical objections. They open opportunities for gathering evidence on several scenarios of ophthalmic care simultaneously, because the compliance of diabetic patients varies [Witkin 84; Dasbach 91]. This automatically generates groups with diverse intensities of ophthalmic care. In experimental studies, such differences would provoke ethical objections, because they then result from official guidelines. Opposite these advantages, there are however some important drawbacks. Cohort studies require at least as much time as experimental studies. No more than (quasi) experiments, can they rapidly answer the central question of this investigation. As compared to other non-experimental studies, cohort studies are relatively expensive, hard to control and not reproducible. They are therefore not suited for this investigation [MacMahon 70:207-40; Kleinbaum 82:47-8, 64-5; Sturmans 84:166-90; Weiss 86:35-8, 72-89, 120-5; Armitage 87:169; Berger 89:136-7].

6.5 Case-Control Studies

This method is also based on observations and causes no ethical problems. Data is gathered from existing records, which reduces the costs as well as the time needed to obtain results. Especially the latter is in this context a decisive advantage. Are case-control studies for that reason an acceptable method? Unfortunately, this is not so. Retrospective studies can only succeed, if a sufficient body of reliable and relevant data has been recorded in the past. This investigation focuses on a technique that has not been applied extensively, until recently. Therefore, existing records do not provide enough information for a convincing case-control study [Mantel 59; MacMahon

70:241-82; Labarthe 79; Kleinbaum 82:51-61, 68-70; Sturmans 84:166-90; Weiss 86:43-6, 101-12; Armitage 87:160-70; Berger 89:137-9].

6.6 Simulation Studies

The experimental and observational methods, presented in the previous sections, cannot analyse at short notice the main issue of this investigation. Can simulations overthrow this barrier? This question evokes arguments pro and con. Let us first consider some advantages presuming that processing is done by computer. Simulations are relatively inexpensive, rapidly feasible and reproducible. Usually, simulation programmes consist of modules, that can be verified both separately and as to their interrelations. Computers may well perform this testing. They can swiftly generate numerous sets of input data, simulate ensuing developments and help analysing results.

Determining the condition of the retina may provide a useful illustration. Most often, this diagnosis is somewhat uncertain, because eye tests are not always perfectly sensitive and specific. Simulations should faithfully imitate diagnostic uncertainty. Computers can help verifying this by generating numbers that reflect the condition of the retina in the eyes of numerous (imaginary) patients. Consequently, these patients traverse the diagnostic module of the simulation, while a supervising module records how many tests are truly or falsely positive or negative. These findings indicate, whether the diagnostic module imitates reality correctly.

Simulations have other important advantages. They do not arouse ethical objections. Furthermore, they permit to tune some factors, like the size and the composition of the population, readily to the requirements of the investigation. Simulations are also able to follow several scenarios simultaneously. Similarly, they enable sensitivity analyses to determine the impact of changing presumptions, logical relations or start values. Many experimental studies have to be content with a rather limited number of patients, which makes the results less convincing. Observational studies may have to face similar limitations. This does not imply however, that these studies are undesirable or superfluous. They form a forefront surveying scientific boundaries to find subjects that deserve large-scale investigations. The current extensive study of the relation between metabolic control and the incidence of complications (DCCT) confirms this. It follows numerous previous investigations of the same issue.

In computer simulations, the population size can easily be adjusted, provided hardware and software specifications are respected. Thus, it is possible to examine larger popu-

lations and to reduce the effect of random fluctuations. In experimental studies of disorders with a limited incidence, the existing number of patients may inhibit testing large populations. The absolute yearly incidence of PDR among Dutch IDDM patients, for instance, is less than some 500. Computer simulations may easily handle cohorts of 10,000 patients.

During experimental or quasi experimental investigations, the study population decreases as a result of mortality, migration or insufficient motivation for further participation. This may affect the characteristics of the remaining population. Let us consider these three factors separately. (1) Patients who die early usually have a poorer health condition and less resistance. Therefore, they are more prone to developing disorders. When they pass away, the relative number of stronger patients increases. The study population then becomes less representative of the general population, presuming it was so at the start of the investigation. On the other hand, the remaining population is longer exposed to developing the disorder. (2) The effect of migration only relates to emigration, which may be international or inter-regional. In the Netherlands, international emigration is at present rather insignificant, while inter-regional migration does not seem to alter considerably the regional age composition [CBS 60..92]. (3) Even after double-blind assignments, patients may discover in the course of experiments to which group they belong. Members of control groups may be less motivated to continue participation. The weight of treatment groups will therefore steadily increase, as investigations go on.

After withdrawals, not only the composition but also the characteristics of the study population may change significantly. The domain of *survival analysis* offers techniques to account for these alterations. However, these techniques are based on the assumption, that the group of withdrawals do not significantly differ from the remaining population [Cox 72; Armitage 87:426; Norušis 90:B-222]. Do longitudinal studies of DR meet this condition? Considering the chronic nature of DM, such studies should cover a considerable number of years. Particularly in the long run, this tries the willingness to participate. Patients with less, or less severe, complications may be more inclined to withdraw. For that reason, it is questionable whether longitudinal investigations of DR meet this condition. Such problems never appear in simulations.

Furthermore, there are other advantages. Once the simulation model is ready, extra computer time suffices to extend investigations to a larger number of years. The length of the period covered by simulations therefore hardly influences the moment, when the outcomes can be published. Thus, the marginal costs of prolonging studies are quite insignificant, which is a substantial asset in analysing chronic diseases. In observa-

tional studies, several distortions, like the *interviewer bias, recall bias* and *selection bias*, may impair data gathering. Simulations are exempt from such distortions, because they record the disease progression objectively and unequivocally. Finally, simulations may use results from several experimental and observational studies to reinforce the basis of the investigation.

Besides assets, there are drawbacks to simulations. Gaps between reality and simulation models cannot be avoided. Until recently, they were ascribed to structural model shortcomings, incorrect parameters and poor estimates of starting situations. Many scientists used to believe, that a deeper insight into underlying relationships plus an improved estimation of parameters and starting conditions would bring simulation models closer to reality. In the end, they thought, models could imitate reality nearly perfectly, like Newton's laws that enable astonishingly accurate astronomical predictions centuries in advance. The *chaos theory* has ended this illusion, at least for the time being. It concerns phenomena where the slightest mutation of initial circumstances may cause dramatic changes in the subsequent course of events, even in the short run [Gleick 87:9-31; Verhoeff 88]. Ipso facto, the measurement of initial circumstances can never be accurate enough to make reliable predictions. The *chaos theory* has become well-known through applications in the field of economics and meteorology during the sixties. Not long afterwards, it was recognised, that this theory also applies to other disciplines, like medicine [Goldberger 90]. Although the impact of the *chaos theory* on this simulation is not clear, this theory advocates considering the simulation results cautiously.

Furthermore, simulations cannot make primary discoveries regarding the pathogenesis and treatment of diseases. The term *primary* relates to findings resulting from newly gathered evidence on the relationship at issue. For that reason, simulations cannot pass judgements on the effectiveness of photocoagulation, until experimental or observational studies provide data. Simulations are well adapted to secondary analyses in the following sense[1]. On the basis of evidence from other investigations, they can imitate various real situations. This enables investigators to gain new insights more speedily and economically. Along this path, the present study strives to improve the understanding of the effectiveness of photocoagulation. Secondary analyses obviously stand or fall with the quality of evidence from primary investigations.

1 According to another subdivision, the ascertaining of new formal relations from existing evidence belongs to secondary analyses, whereas simulations form tertiary analyses.

The latter should present reliable data on the following issues: (1) the mortality of the general population; (2) the relative life expectation of diabetic patients related to the severity of DR, including the condition *"no DR"*; (3) the incidence or prevalence of IDDM, NIDDM-a and NIDDM-b; (4) the incidence or prevalence of DR, PDR, ME, moderate vision and blindness related to the type of DM; (5) the quality of different diagnostic tests; (6) the success rates of various laser treatments; (7) the financial aspects of ophthalmic care, disability facilities, social security and productivity losses as a result of visual impairment.

Simulations are also quite distant from classical methods. This may impede the willingness to accept the outcomes. Finally, simulations must refer to contemporary techniques, circumstances and conceptions, while producing scenarios for the future.

6.7 Discussion

Do these limitations and drawbacks render simulations ill-suited for analysing the central research issue? This investigation does not aim at unfolding primary relations on the effectiveness of photocoagulation. Therefore, a secondary analysis is quite legitimate. The remaining drawbacks chiefly concern the uncertainty margin of outcomes, the size of which notably depends on the following factors: (1) the reliability of evidence; (2) the technical quality of the simulation; (3) the structure of the simulation model; and, in case of forecasts, (4) future developments in medical technology, prices, productivity and social security. Sensitivity analysis is a powerful instrument to examine the factors (1), (2) and (3). Even in the phases of model construction and implementation, it can already give an impression of the corresponding uncertainty margin. The test of factor (4) is only feasible towards the end of the period covered by the simulation model. For this reason, the actual uncertainty margin is partly unpredictable, when the model generates forecasts.

Opposite the actual margin, there is the margin considered acceptable by the investigator or the reader consulting the results. The latter margin depends on several factors, like the urgency of the problem at issue, the effectiveness of today's technology to solve the problem and the merits of other simulations. That margin also relates to personal factors, like one's general attitude towards simulations and the degree of agreement between one's own views or expectations and the outcomes of a specific simulation. General and individual factors therefore jointly determine the size of the acceptable uncertainty margin, that differs from person to person. Finally, the acceptable and the estimated actual margins are compared. With respect to a specific simulation, this

assessment will be associated with dissimilar balances, forming a spectrum embracing declared opponents and proponents.

Which implications has this for the present study? The general drawbacks and limitations of simulations do not constitute an absolute methodological barrier for developing a simulation aimed at solving the central research issue. However, not everyone will therefore accept the results. This scepsis emphasises the relativity of the simulation and may therefore also be useful for advocates of this technique.

Nonetheless, studies on the effectiveness of ophthalmic care for diabetic patients are required urgently, because existent ophthalmic techniques can safeguard numerous patients, in a confined and well-delimited risk group, from serious health disorders. In other words, these patients face a substantial problem, but it is solvable, at least to a considerable extent. Simulations are also indispensable, because other methods are at short notice unable to provide insight into the effectiveness of different scenarios of ophthalmic care. They are unique in enabling large patient groups rapidly to traverse various ophthalmic regimes without ethical objections, even if many years are to be covered. The tightening up of the privacy legislation, that notably finds expression in the *informed consent,* heightens the barriers for other methods and renders simulations comparatively more attractive.

As mentioned before, simulations can also provide maximum command of external circumstances, including compliance. They avoid problems that *survival analysis* does not solve. Finally, simulations do not interfere with studies along classical lines. Hence, it seems legitimate to use a simulation model for examining the central issue of this investigation, as well as the related questions.

7

A Continuous Simulation

7.1 Introduction

The two simulations presented in chapter four generate Markov processes covering a rather limited number of discrete health states. Consequently, they may approximate the progression of DR just roughly. A continuous simulation should offer a more realistic imitation of retinal developments, ophthalmic examinations and laser treatments. However, the consulted technical literature offers no examples of continuous simulations. Therefore, a special technique was developed. The next sections present its essentials and highlight the contrast with discrete simulations. Then, chapter eight depicts the structure of the simulation.

7.2 Logistic Approximation of Prevalence

Starting from epidemiologic and medical sources, the simulation examines the progression of DR in a cohort of diabetic patients. Most studies characterise that process with a few percentages. Frequently, they present statements like the following.

X years after the onset of IDDM, y% of the study population suffers from DR.

These observations usually accentuate some characteristic moments in the disease progression, such as the year when half the study population faces DR or the time when the prevalence reaches its maximum. Most epidemiologic studies on ME and PDR present similar data. Hence, they do not give sufficient support to follow DR continuously. This calls for approximations.

The first approximation concerns the construction of prevalence functions from a set of points. Polynomials, of a degree chosen by the investigator, offer well-known approx-

imations [Press 89:87-115]. Their accurateness depends on the number of data points. Is this technique suitable to trace the prevalence of retinal disorders from the onset of DM until the death of all the study population, if only a limited set of data is available?

$$y = c_0 + c_1 x + c_2 x^2 + \cdots + c_n x^n \qquad (7.1)$$

Some imaginary data on the prevalence of DR, represented in the column *actual prevalence* of table 7.1, may assist in answering this question. This data roughly corresponds with the actual prevalence of DR. Approximation [1] calculates a polynomial of degree three based on five actual prevalence rates for the years 0, 5, ... 20. Formula 7.1 introduces a polynomial of degree n. In this example, x represents the duration of IDDM and y the estimated prevalence.

The coefficients c_0, c_1, c_2 and c_3 in approximation [1] yield estimates that correspond satisfactorily with the actual prevalence rates during the years 0 to 20. Later, the extrapolation becomes meaningless: 6% after 30 years, −437% after 40 years and −1,422% after 50 years. Approximation [2] rests on six actual rates, including year 40. Its forecast for year 50 is less unrealistic, but its interpolation is poor in the years 0 (−2%) and 30 (147%). Approximations with polynomials of degree two produce superior estimates for later years. Nevertheless, they are left aside, because several negative estimates appear for earlier years. The next paragraph explains, that the relationship between prevalence rates and the duration of DM is far from linear. For that reason, a polynomial of degree one was not examined. This example suggests, that polynomials may approximate the prevalence of DR inadequately.

Studies on the progression of DR reveal, that the prevalence of retinal disorders roughly follows a logistic, or S-shaped, curve, if it is related to the duration of DM [cf. Palmberg 81; Klein 84b, 84f; Dwyer 85; Javitt 89]. At the onset of DM, the prevalence rates are virtually zero. Then, they increase slowly. In the third phase, the rates rise sharply. On approaching their maximum, their growth weakens. Finally, the prevalence rates may drop slightly after reaching their top.

Duration of IDDM (years)	Actual prevalence	Estimated prevalence [1]	Estimated prevalence [2]
0	0.00	0.00	-0.15
5	0.02	0.00	0.18
10	0.30	0.33	0.46
15	0.75	0.73	0.68
20	0.98	0.98	0.86
30		0.06	1.04
40	0.99	-4.37	1.02
50		-14.22	0.78

[1] based on prevalence in year 0, 5, 10, 15 and 20

[2] based on prevalence in year 0, 5, 10, 15, 20 and 40

	Polynomial coefficients	
c0	0.00429	-0.02000
c1	-0.04871	-0.00666
c2	0.01129	0.00511
c3	-0.00032	-0.00011

Table 7.1 - Actual prevalence of DR versus estimates by Chebyshev-polynomial[1]

Formula 7.2 proposes a logistic function for the prevalence of DR among IDDM patients: P(DR | IDDM). The definition of prevalence implies: $0 \le P(DR \mid IDDM) \le 1$. As $e^x > 0$ $\{-\infty < x < +\infty\}$, the denominator in formula 7.2 may have any value between 1 and $+\infty$. Therefore, the prevalence ranges from 0 to Max_{DR}, which represents the maximum prevalence of DR $\{0 \le Max_{DR} \le 1\}$.

$$P(DR \mid IDDM) = \frac{Max_{DR}}{1 + e^{a_{DR}(t - h_{DR})}} \tag{7.2}$$

The coefficient a_{DR} determines the steepness of the curve. The variable t indicates the time since the onset of DM, while the constant h_{DR} relates to the moment, when the prevalence reaches half its maximum, Max_{DR}. Because $a_{DR} < 0$, e has a positive exponent, provided $t < h_{DR}$. The curve reflects an increasing sequence.

1 The coefficients were determined with the modules *COMMON.INC*, *LEAST.INC*, *LEAST.PAS* and *POLY.LSQ* of the *Turbo Pascal Numerical Methods Toolbox* by *Borland International Inc.*, Scotts Valley CA, 1986. These modules, written in *Turbo Pascal 3.0 (MS-DOS)*, were adapted to be executed on an *Apple Macintosh* computer.

As mentioned previously, publications on retinal disorders usually offer a small set of prevalence rates. Hence, they can only give rough views on the disease progression. Some sources specify larger sets of rates [Klein 84b, 84c]. In these publications, several graphs represent considerable fluctuations of prevalence rates. Klein et al. indicate for instance, that the prevalence of PDR among juvenile diabetic patients decreases some twenty years after the onset of IDDM within three years from about 60% to approximately 45% [84b]. In other words, a quarter of the patients with PDR benefit by regression, provided there are no new cases of PDR during those three years. If this unrealistic assumption proves false, an even larger proportion of the patients with PDR experience regression[2]. Observations by Beetham of 351 patients with PDR, including 196 (55.8%) IDDM patients, reveal that 8 (2.3%) patients experience regression for more than four years, 6 (1.7%) for three years, 3 (0.9%) for two years, and 18 (5.1%) for one year [63]. More recent studies do not mention higher regression rates. Therefore, the regression rate mentioned by Klein et al. may barely be representative of the development of PDR. Their findings could be connected with the limited size of the population giving coincidence more weight. This example illustrates, that an approximation, for instance with a logistic function, may also prove useful, when a rather large set of rates is known, namely to smooth unrealistic fluctuations of prevalence rates.

In returning to logistic approximations, the question arises how to estimate the three parameters in formula 7.2: Max_{DR}, a_{DR}, h_{DR}. It may seem self-evident to use the logistic regression module of software for statistical analysis. Provided the number of data equals the number of unknown variables, the parameters may also be determined by solving a set of equations. Table 7.2 illustrates both techniques using the example of table 7.1. It provides six data on the actual prevalence of DR, each consisting of one pair (t, P(DR | IDDM)). Three of these six pairs are needed to evaluate the three unknown parameters using a set of three equations. These parameters determine a function, that passes through the points corresponding to the three data pairs. This is generally not the case for points related to other data pairs. Hence, considerable gaps might appear between actual and estimated prevalence rates. Adjusting some values of the data pairs may reduce such discrepancies. The three parameters in the second column of table 7.2 are based on the actual values of the pairs two (5, 0.02) and five

2 The factor *mortality* is not considered separately for the following reason. Among IDDM patients, the onset of DM occurs on average at the age of 14.5 years. Twenty years later, hazard rates are still relatively small. Patients suffering from PDR may then have slightly higher hazard rates, but they are not numerous enough to modify the outcome of these rather crude calculations significantly.

(20, 0.98) - indicated in the third column of the table - and on an adjusted value of pair four (15, 0.82), instead of (15, 0.75). Is this crude approximation acceptable in the presence of generally accepted methods, like logistic regression?

Duration of IDDM (years)	Estimate based on system of equations	Actual prevalence	Estimate based on logistic regression
0	0.00	0.00	0.00
5	0.02	0.02	0.03
10	0.24	0.30	0.24
15	0.82	0.75	0.77
20	0.98	0.98	0.97
30	0.99		1.00
40	0.99	0.99	1.00
50	0.99		1.00
Max_{DR}	0.9937	α	0.4702
a_{DR}	-0.5437	β	-5.8538
h_{DR}	12.1457		

Table 7.2 - Actual and estimated prevalence of DR[3]

Table 7.2 confronts estimates by both techniques. The second column uses the method introduced in the previous paragraph, the fourth column logistic regression. In the neighbourhood of year 15, logistic regression offers superior results. In most other years, the cruder technique yields closer approximations. Objective criteria give insufficient support for determining which technique presents the better fit in this context. When developing simulations, it therefore seems worthwhile to resort to both techniques and to determine empirically which one generates better estimates. Using a set of equations probably produces superior results, if the number of available data pairs on actual prevalence rates roughly corresponds to the number of unknown parameters. Logistic regression may be more profitable, when a considerably larger data set is accessible. This example stands somewhere midway between both extremes.

3 The set of equations were solved using *Mathematica 1.2, Wolfram Research Inc.*, Champaign IL, 1989. The logistic regression parameters were determined with the module *Logistic Regression Analysis, SPSS 4.0.1, SPSS Inc.*, Chicago IL, 1990.

Although logistic regression forms a widely accepted approximation method, its blind application may also be hazardous for other reasons. (1) It seems prudent to compare several studies, because numerous epidemiologic investigations of DR concern rather small populations. (2) Insights into the pathogenesis should guide this comparison, as the previous remarks on the likelihood of PDR regression illustrate. (3) In epidemiologic studies, the prevalence rates of retinal disorders usually reflect the condition of each patient's poorer eye. The simulation describes the condition of every eye separately. If the empirically found prevalence rates were applied without adjustments, the simulation would be far too pessimistic. In practice, testing by experience emerges as quite a feasible technique for determining these adjustments, that will be discussed more extensively later on. (4) The empirically sounded prevalence rates of blindness and moderate vision relate to each patient's better eye. They also require adjustments, preferably by experience. (5) Most prevalence rates of retinal disorders have a ceiling beneath 100%. In logistic regression this causes complications, that the next paragraph analyses rather generally.

$$P = (1 + e^{-(\alpha t + \beta)})^{-1} \tag{7.3}$$

In formula 7.3, the independent variable is t, *the duration*, while the dependent variable is P, *the likelihood of a disorder*. The parameters α and β, respectively the slope and the intercept of the line $\alpha t + \beta$, are estimated via logistic regression. In formula 7.3, the numerator equals 1, whereas in formula 7.2, it may have any value from the interval [0, 1]. In other words, $P < 1$ in formula 7.3 and $P(DR \mid IDDM) < Max_{DR}$ in formula 7.2. Therefore, logistic regression is an adequate technique, when the chance of some disorder follows an S-curse through time from 0% to 100%. For most retinal disorders among diabetic patients, however, the maximum prevalence rate is significantly less than 100%.

In that case, logistic regression may only be effective, after the data have been transformed. This process is illustrated by assuming, that the findings mention for each patient separately the duration of DM and the presence of the disorder. The analysis consists of six steps. (1) The empirical data are assigned to duration categories. (2) In each category, the prevalence rate is calculated. (3) The maximum prevalence rate Max_P is determined. (4) The rates calculated at step (2) are transformed linearly from interval (0, Max_P) to interval (0, 1) through multiplication by the factor $1 / Max_P$. (5) Logistic regression is applied to the transformed data. (6) In the regression formula, that is comparable to formula 7.3, the numerator is replaced by Max_P.

As such, this transformation is unlikely to cause technical complications. However, the data does not always give sufficient support for determining the factor 1 / Max_P exactly. Different studies reveal strikingly divergent prevalence rates of retinal diseases, particularly 30 to 40 years after the onset of DM, when the prevalence rates of most disorders approach their maximum. By that time, the number of patients has fallen considerably because of mortality. How much importance should be attached to outliers in that phase? Mathematical smoothing techniques, like fast *Fourier*-transformations, may render such outliers less conspicuous [Press 89:543-6]. However, the flattening degree depends on arbitrary choices. Subjective factors therefore affect the value of Max_P after smoothing. In other techniques, the value of the transformation factor 1 / Max_P also partly depends on personal preferences.

Linear regression is one of these alternatives. This technique can also determine the coefficients α and β for every acceptable value of Max_P $\{0 \leq Max_P \leq 1\}$. First, Max_P is substituted in the numerator of formula 7.3. That formula is then rephrased as formula 7.4.

$$-\ln\left(\frac{Max_P}{P} - 1\right) = \alpha t + \beta \tag{7.4}$$

Similarly to logistic regression, the data is categorised according to duration for determining Max_P. The latter calculation causes essentially the same arbitrariness as mentioned in the context of logistic regression. Then, the categorised data is processed with linear regression on the basis of formula 7.4. As Max_P is constant for each specific data set, the left term of formula 7.4 is essentially comparable to y in the formula $y = \alpha t + \beta$, where y has the following relation to P.

$$y = -\ln\left(\frac{Max_P}{P} - 1\right) \tag{7.5}$$

In other words, y is a strictly monotonously increasing function of P $\{0 < P < 1;$ $P < Max_P \leq 1\}$. Consequently, formula 7.5 relates each P to one value of y and each y to one value of P. After determining the coefficients α and β by linear regression, this technique expresses a relationship between t and P. The problems related to Max_P illustrate again, that the simulation cannot rely blindly on a generally accepted approximation technique and that prevalence functions cannot be derived directly from empirical evidence. Instead, data should be gathered from different studies and weighted arbitrarily. Where data is lacking, estimates should fill gaps. This obviously may cause errors. To minimise these, an extensive literature study, mentioned in part A, preceded the development of the simulation.

$$P(DR|IDDM)=\begin{cases} \dfrac{Max_{DR}}{1+e^{a_{DR}(t-h_{DR})}} & (0\le t\le t_o) \\ \dfrac{Max_{DR}}{1+e^{a_{DR}(t_o-h_{DR})}}-b_{DR}(t-t_o) & (t>t_o) \end{cases} \tag{7.6}$$

Bibliographical sources reveal, that S-curves usually approximate the presence of a retinal disorder adequately, until the prevalence reaches its maximum. Thereafter, the prevalence may decline slowly, as some studies indicate [e.g. Klein 84b]. S-curves then provide inadequate support. Hence, 7.6 holds two formulas to describe the likelihood of DR. The value of t_o is such, that P virtually equals Max_{DR} for $t = t_o$, according to the first equation. After the ceiling, the second equation presents a line with slope $-b_{DR}$ $\{b_{DR} \geq 0\}$. Instead of an S-curve, the simulation might use any other function that describes the prevalence adequately. Should future epidemiologic investigations reveal that other functions give a better fit, modifying a smaller module may suffice for incorporating new insights in the model.

7.3 Four Aspects of the Retina

The simulation uses the approximation method presented in the previous section to observe the condition of four aspects of the retina for each patient and each eye separately: (1) the macula, (2) the peripheral area of the retina - for the sake of brevity named retina - plus (3) central acuity and (4) peripheral vision. This subdivision relates to the following relationships. (a) The condition of the macula is the principal determinant of central acuity, while (b) the condition of the peripheral retina is decisive for peripheral vision. Section 7.6 will explain how the simulation implements these two relationships in assigning values to variables.

According to medical practice, the model represents the quality of retinal aspects by real numbers from the interval (0, 1) [4], which makes the simulation (pseudo-) continuous. This typification may raise objections. Modern desk-top computers, including

4 Medicine uses the interval [0, 1), which includes death. Regarding eye aspects, the simulation leaves the value 0 out of consideration for several reasons. (a) The values of eye aspects are only relevant for living patients. With these values, the simulation model determines the mortality rates as well as the effectiveness of ophthalmic tests and treatments. (b) The simulation uses logistic transformations between the intervals (0, 1) and $(-\infty, +\infty)$. The conversion formulas are not defined for border values.

the machines that have supported this investigation, store data digitally. They can only represent a finite set of distinct numbers, which inhibits for instance symbolising all real numbers from the interval (0, 1). Are such computers capable of processing continuous simulations? Moreover, the model assigns new values to retinal aspects only once every three months. Does this method suit a continuous simulation?

In answering the first question, it is worthwhile to notice, that all measurements, including retinal measurements, have a limited precision. If the recording device represents that precision completely, the registered precision equals the realised precision. Programming languages for digital computers define real data types, that accommodate the precision of retinal measurements without restriction. Therefore, the inability of digital computers to represent all real numbers in the interval (0, 1) constitutes no bottleneck.

Regarding the second question, it should be emphasised, that this simulation does not analyse the disease progression but the effectiveness of ophthalmic care strategies. Hence, it does not focus on the condition of the retina as such but rather on perceptions of that condition by ophthalmologists. These perceptions have an intermittent nature, because patients are not diagnosed and treated constantly, but periodically. For that reason, the simulation may confine itself to offer periodically, at the time of diagnosis and treatment, a description of the retinal condition. If the accuracy of this description corresponds with the accuracy of ophthalmologic tests, the simulation may imitate the effectiveness of eye examinations and treatments realistically. The likelihood of diagnostic misclassification, for instance, depends on the distance between the actual condition and the border value of two subsequent categories. Analogically, treatment success chances are related to the retinal condition.

A realistic imitation of these events requires distinguishing more than four or five states in the progression of DR, as the simulations by Javitt et al. [89, 90, 91] and Dasbach et al. [91] do. For that reason, this simulation uses real numbers, that allow recording with actual measurement precision. The frequency of value assignments to retinal aspects equals the frequency of eye tests for the highest risk patients in the scenario with the most intensive eye care. Hence, these values are generated at least as frequently as patients have tests or treatments. In all scenarios and for all living patients, these values constitute the basis for determining individual hazard rates, which section 8.7 will explain further.

Once every three months, the simulation model assigns new values to all retinal aspects for every living patient. As later sections will explain, this frequency is sufficient in

relationship to examinations, treatments and hazard rates. It has already been pointed out, that the simulation provides adequate precision. From the perspective of the objectives presented in chapter five, this simulation may therefore be considered continuous. However, this nature does not harmonise with evidence. Epidemiologic investigations of DR mention prevalence and incidence rates for several disease categories. Section 3.3 has indicated that different authors use different category distinctions. Therefore, it is essential to choose a category division that accommodates various findings from different sources. From these categorised data, a continuous representation is then derived.

Macula	Peripheral retina	Central acuity	Peripheral vision
no DR	no DR	Good	Good
BR	BR	Moderate	Moderate
ME	PDR	Blind	Blind

Table 7.3 - Four retinal aspects arranged in three quality categories

Table 7.3 presents three quality categories for four retinal aspects. Data arranged in narrower categories can easily and virtually unequivocally be assigned to a specific category of this rough subdivision, mentioned before in section 3.3. For each eye, this subdivision provides an answer to the next questions. (a) Has DR developed? (b) Has high-risk DR developed, requiring laser treatment? (c) Has moderate vision occurred? (d) Is the eye blind?

Macula	Peripheral retina	Central acuity	Peripheral vision
>2/3	>2/3	>20/40	>20/40
≤2/3 and >1/3	≤2/3 and >1/3	≤20/40 and >20/200	≤20/40 and >20/200
≤1/3	≤1/3	≤20/200	≤20/200

Table 7.4 - Quantification of three quality categories for four retinal aspects

Table 7.4 quantifies these categories. Today, it is quite common to express visual acuity in quotients. If visual acuity equals 6/60 for instance, the eye is able at a distance of 6 meters to read letters, that are readable at 60 meters with normal vision. This corresponds to 20/200, in case distances are measured in feet. An older, yet frequently used, scale is the *échelle de Monnoyer*, that values the normal vision of healthy adults at 1 and complete blindness at 0 [acuité visuelle]. Transforming these two quotients to the *échelle de Monnoyer* is straightforward. Both 6/60 and 20/200 correspond to 0.1. Davis et al. [79] and Herman [90] also use 20/40 and 20/200 as upper limits of moderate vision and blindness. The latter limit is based on the following definition of binocular blindness.

Visual acuity of 6/60 (20/200) or less in the better eye with best correction, or visual acuity of more than 6/60 if the widest diameter of the field of vision subtends an angle no greater than 20 degrees
[National Institute of Neurological Diseases and Blindness 1964; quoted by: Goldstein 80:34]

The quantification of BR, ME and PDR is arbitrary. However, the limits in table 7.4 seem to be consistent with descriptions of these disorders and with ordinal classifications used by investigators [Klein 84b, 84g]. Apart from that, different limits would not alter the simulation significantly, provided these limits are situated well within the interval (0, 1). With the limit values presented in table 7.4, the next section specifies how categorised data can be transformed to a continuous distribution.

7.4 Logistic-Normal Distribution

The simulation studies the development of DR in a cohort of diabetic patients, presuming that health conditions are always normally distributed. This hypothesis is disputable. The set of evidence on this subject in medical publications is too small to prove, that this assumption is realistic. However, the data does not point to another distribution. Then, why does this simulation choose a normal distribution? Simply, because most characteristics of the human body are normally distributed. The body length is a well-known example.

Apart from these epidemiologic considerations, some technical arguments also justify the choice of a normal distribution. There are several generally known and accepted algorithms for processing sets of normally distributed numbers. Implementing these algorithms in computer programmes requires rather little effort. However, the normal distribution as such cannot represent the health condition, as the first relates to the interval $(-\infty, +\infty)$ and the second to the interval (0, 1). Fortunately, some elementary logistic transformation formulas exist, like formula 7.7 that handles the conversion from the first to the second interval.

$$x = \left(1 + e^{-y}\right)^{-1} \qquad \{y \in \mathbf{R} \mid -\infty < y < +\infty\} \tag{7.7}$$

Formula 7.8 manages the transformation in the opposite direction.

$$y = \ln\left(\frac{x}{1 - x}\right) \qquad \{x \in \mathbf{R} \mid 0 < x < 1\} \tag{7.8}$$

Here, y is the logit of x [Houwelingen 88]. These two transformation formulas unequivocally relate each real number in one interval to a specific real number in the other interval. In other words, each y is associated with one x according to 7.7 and each x with one y according to 7.8.

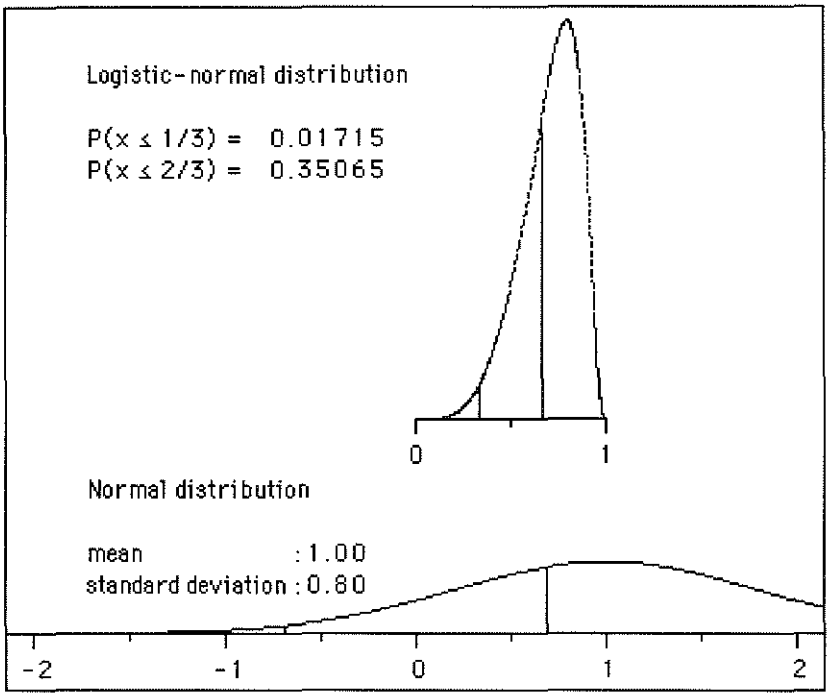

Figure 7.1 - Probability density curve of a logistic-normal and a normal distribution

Figure 7.1 illustrates these transformations for a cohort of diabetic patients. At some moment, the following prevalence rates prevail for the peripheral retina of the left eye: PDR 1.715%, DR 35.065%. Eyes with PDR are a subset of eyes with DR. The parameters of the normal distribution are derived from these two percentages, in considering each of the latter as the probability of drawing values smaller than a specific value. According to tables for the standard-normal distribution, these two percentages have the following z-values: –2.1163 and –0.3836. Applying formula 7.8 discloses, that the critical values of the peripheral retina, 1/3 and 2/3, respectively correspond to –0.6932 and +0.6932 in the interval $(-\infty, +\infty)$. The second graph in figure 7.1 repre-

sents each of these values by a vertical line. The mean μ and the standard deviation σ are determined by solving the following set of equations[5].

$$\begin{aligned} -0.6932 &= \mu - 2.1163\sigma \\ 0.6932 &= \mu - 0.3836\sigma \end{aligned} \tag{7.9}$$

The solution of this equation set is: $\mu = 1$, $\sigma = 0.8$. The second graph in figure 7.1 represents the probability density function of the normal distribution with these parameters.

$$\text{(a)} \quad y = \ln\left(\frac{x}{1-x}\right) \qquad \{x \in \mathbf{R} \mid 0 < x < 1\}$$

$$\text{(b)} \quad f_{\mu,\sigma}(y) = \frac{1}{\sigma\sqrt{2\pi}} e^{-0.5\left(\frac{y-\mu}{\sigma}\right)^2} \qquad \{\mu,\sigma \in \mathbf{R} \mid \sigma > 0\} \tag{7.10}$$

$$\text{(c)} \quad g_{\mu,\sigma}(x) = (2 + e^{y} + e^{-y})\, f_{\mu,\sigma}(y)$$

The formulas 7.10 indicate in three steps, how the probability density function of a logistic-normal distribution is determined. (a) From any x in the interval (0, 1), the logistic transformation formula assesses the corresponding y in the interval $(-\infty, +\infty)$. (b) With the previously solved μ and σ, the probability density $f_{\mu,\sigma}(y)$ is then calculated in the normal distribution (μ, σ) for y. (c) The last formula calculates the probability density $g_{\mu,\sigma}(x)$ in the logistic-normal distribution for x.

The next property is characteristic for logistic-normal distributions. In any logistic-normal distribution, the area under the probability density curve to the left of any acceptable x_0 equals the area under the probability density curve to the left of y_0 in the corresponding normal distribution, provided y_0 is the transformation of x_0 through formula 7.8. Formula 7.11 formalises this property.

$$\int_0^{x_0} g_{\mu,\sigma}(x)dx = \int_{-\infty}^{y_0} f_{\mu,\sigma}(y)dy \quad \forall \quad y_0 = \ln\left(\frac{x_0}{1-x_0}\right) \quad \{x_0 \in \mathbf{R} \mid 0 < x_0 < 1\} \tag{7.11}$$

5 For any y, the following equality is valid: $z = (y - \mu) / \sigma$. $\{y \in \mathbf{R} \mid -\infty < y < +\infty\}$

By this property, the logistic-normal distribution suits the data of the example. Hence, it is easily understandable, that 1.715% of the total area under the curve in the first graph of figure 7.1 is situated to the left of $x = 1/3$ and 35.065% to the left of $x = 2/3$ [Johnson 70a:40-53; Doubilet 85]. The choice of a logistic-normal distribution resulted from a comparative analysis of several continuous univariate distributions. At first, the β-distribution seemed quite interesting. It is determined by two parameters, like normal and logistic-normal distributions [Johnson 70b:37; Lindgren 76:329]. Moreover, β-distributions are confined to the interval (0, 1). Is was however impossible to write a programme, that determines both parameters of the β-distribution unequivocally on the basis of the probabilities of drawing numbers smaller than two specific values [starting point: some routines by Press 89:175-89].

The logistic-normal distribution curve may have a particular shape. Figure 7.2 presents an example, where the prevalence rates of blindness and moderate vision equal 10% and 30% respectively. The limit values presented in table 7.4 imply, that $0 < x \leq 0.1$ covers 10% of the area under the probability density curve, $0.1 < x \leq 0.5$ 20%, and $0.5 < x < 1$ 70%. The probability density curve therefore reaches higher values in the first and the third interval, as compared to the second interval. This explains the J-shaped curve in figure 7.2.

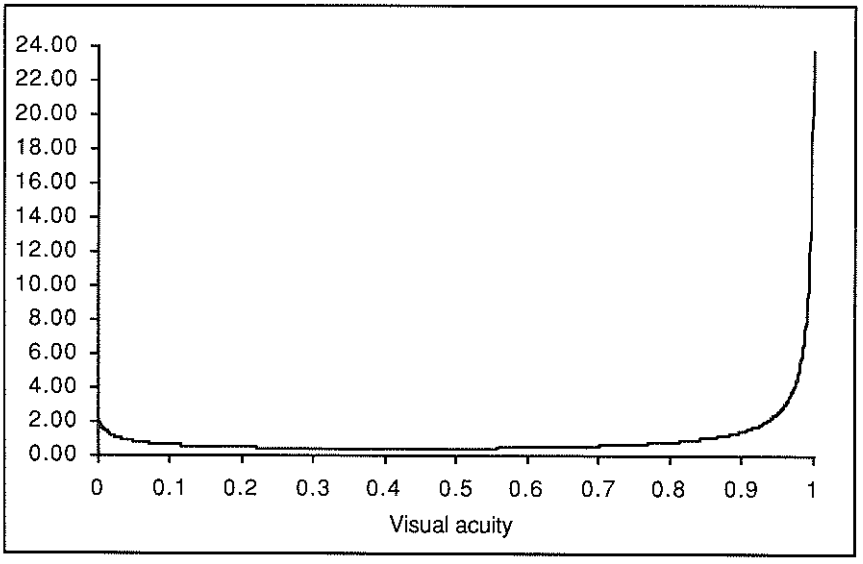

Figure 7.2 - Probability density curve of some logistic-normal distribution

7.5 Progression per Retinal Aspect in a Cohort

Section 7.2 has pointed out, that the simulation approximates the observed prevalence rates of DR, moderate vision and blindness with logistic functions. These functions give unequivocal information on prevalence rates for any acceptable value of t, the duration of DM, provided t is the independent variable. By contrast, empirical data usually indicate a sparse set of prevalence rates, for instance for x, y, and z years after the onset of DM. This is illustrated with the following - imaginary - findings on the prevalence of DR among IDDM-patients: 0 years after onset: 0 %; 6 years: 12%; 10 years: 50%; and 20 years: 100%. If formula 7.2 is used, this logistic function may have the following parameters: $Max_{DR} = 1$, $a_{DR} = -0.5$, $h_{DR} = 10$.

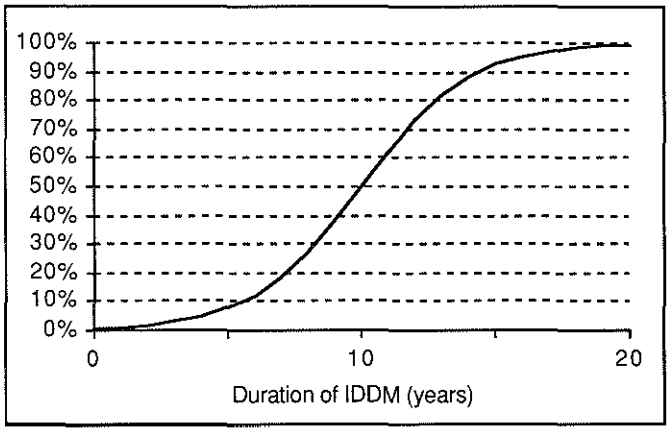

Figure 7.3 - Approximation of prevalence rates by a logistic function

Figure 7.3 presents this function graphically for the years 0 to 20 after the onset of IDDM. The prevalence rates equal 100% in subsequent years, because DR is an irreversible disorder. For each moment after the onset of DM, this logistic function indicates a specific prevalence rate. This property is particularly interesting for this simulation, that assigns new values to the four retinal aspects of all living patients periodically. For practical reasons, each period in the simulation covers three months. However, the continuous nature of the logistic function allows any other period length $\{> 0\}$.

At any moment and for every retinal aspect, logistic functions accommodate the simulation with two prevalence rates related to the quality categories presented in the tables 7.3 and 7.4. The prevalence rates of DR and ME characterise the condition of the

macula, where the second disorder is seen as a subset of the first. Similarly, the prevalence rates of DR and PDR mark the state of the peripheral retina. For the two aspects of vision, there are prevalence rates of moderate vision and blindness. The second category is again a subset of the first. Consequently, the simulation has always precise information about the area under the probability density curve to the left of the two critical values for each retinal aspect. By the method illustrated in section 7.4, these two probabilities determine the parameters of a logistic-normal distribution for each retinal aspect once every three months.

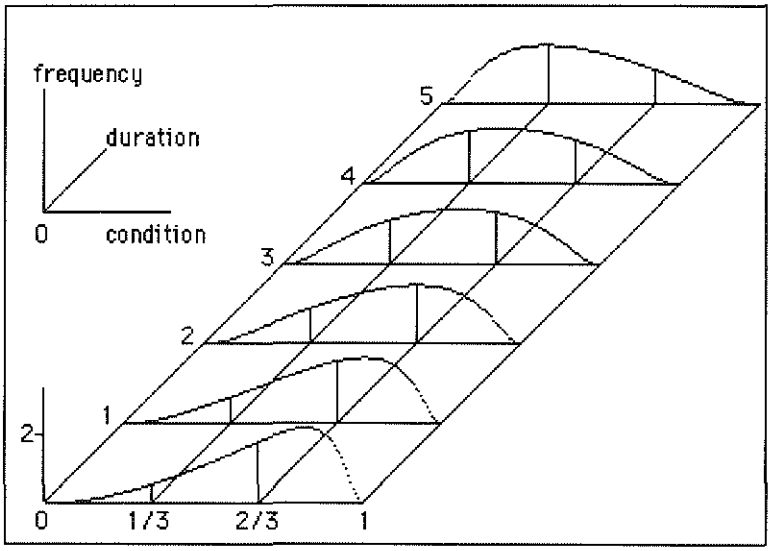

Figure 7.4 - Prevalence history of DR in the peripheral retina

Figure 7.4 illustrates, how the simulation describes the prevalence history in a cohort. The axis *condition* depicts the previously mentioned interval (0, 1). In the plane *(condition, duration)*, lines are drawn parallel to the axis *duration* to represent the eye conditions 1/3 and 2/3 respectively. These two lines indicate the upper limits of two disorders, namely DR and PDR, because this graph concerns the peripheral retina. Finally, the graph presents six probability density functions for the periods 0 to 5. For the sake of clarity, they reflect extraordinarily rapidly rising prevalence rates of DR and PDR. They are not related to the earlier example in this section.

In figure 7.4, the prevalence of DR and PDR is comparatively insignificant in period 0. Hence, there are high frequencies to the right of the point (2/3, 0, 0). From 2/3 to 1/3, frequencies fall. The area under the curve in the interval (1/3, 2/3] is unmistakably smaller than the area related to the interval (2/3, 1). In other words, only a

minority of the population suffers from BR. To the left of the point (1/3, 0, 0), the curve nearly coincides with the axis *condition*, as only a few patients face PDR. It may be needless to say, that the areas to the left of the points (2/3, 0, 0) and (1/3, 0, 0) correspond to the prevalence rates derived from the logistic curves for DR and PDR.

In period 1, both logistic functions indicate higher prevalence rates. Consequently, more patients suffer from DR and PDR than in period 0. This explains the shift of the probability density curve. The area for the interval (2/3, 1) decreases, because a smaller fraction of the population remains free from DR. On the contrary, the area for the interval (1/3, 2/3] grows. Hence, a larger part of the population suffers from DR. This comment also applies to the interval (0, 1/3]. In period 1 more patients have PDR. Every year, a similar shift of the probability density curve occurs. Gradually, the number of patients to the right of the border line through (2/3, 0, 0) decreases, while more and more patients reach the central area between the upper limits of DR and PDR. Simultaneously, there is an outflow to the area representing the prevalence of PDR. The point of gravity of the probability density curve therefore gradually shifts by way of BR towards PDR. Figure 7.5 illustrates the same course of events as figure 7.4, but rather in perspective. In both figures, the axes have the same meaning.

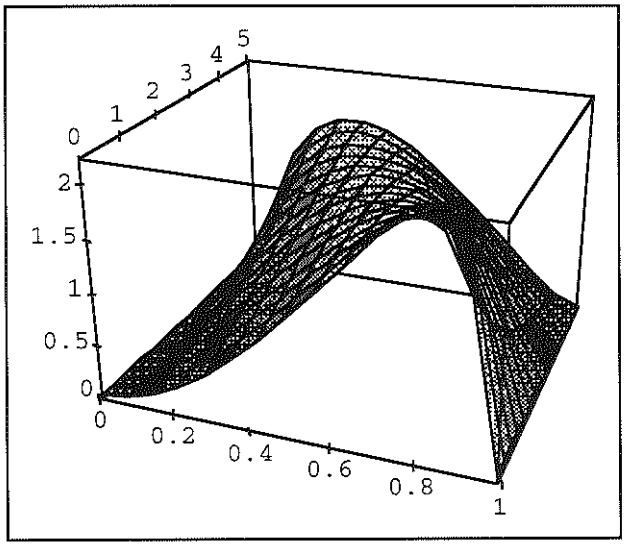

Figure 7.5 - Prevalence of DR in peripheral retina (in perspective)

This method also permits observing other retinal aspects, because the simulation always has adequate information on two prevalence rates. In relation to vision, it suffices to adapt the critical values to the limits presented in table 7.4 (20/200 and 20/40).

7.6 Progression per Retinal Aspect per Eye

For each retinal aspect and in every period, the simulation commands the mean μ and the standard deviation σ of a normal distribution, thanks to epidemiologic data and approximation techniques. By the formulas 7.10, the parameters μ and σ determine unequivocally the probability density function of the corresponding logistic-normal distribution. For a specific period, this function indicates, how the various conditions of a particular retinal aspect are distributed in the cohort. As μ and σ are known for any analysed period, it is possible to trace how that distribution shifts in the course of time. Illustrations, like the figures 7.4 and 7.5, give an impression of that movement in one glance. Although this overall view may be most interesting, the simulation also enables tracking each retinal aspect in every eye individually. What method does it use for that purpose?

$$y_{t,s,p,e,a} = z_{t,s,p,e,a}\sigma_{t,a} + \mu_{t,a} \tag{7.12}$$

At the start of the simulation, a random number z is drawn from the standard normal distribution for every eye and for each retinal aspect. According to formula 7.12, this number, as well as μ and σ, determine the value y of this retinal aspect in the interval $(-\infty, +\infty)$. Five subscripts give formula 7.12 a more general meaning: (t) time, (s) sex, (p) patient number, (e) eye, (a) retinal aspect. As opposed to y and z, μ and σ have only two subscripts: t and a. This means implicitly, that epidemiologic data do not offer enough ground for differentiating the progression of DR according to gender or to left and right eyes. The resulting set of y's will approximately have the normal distribution (μ, σ), provided the z's are drawn for a large number of patients by a high-quality random generator [Putten 79:28-9; Knuth 81:9-37; Press 89:212-26; Rugg 89:95-9]. Transforming the y-set by formula 7.7 yields a set of x's in the interval (0, 1). If this set concerns the retinal aspect *peripheral retina*, the fraction of values $< 1/3$ nearly equals the observed prevalence of PDR and the fraction of values $< 2/3$ the observed prevalence of DR, including PDR.

The random number generator[6] has a crucial role in this process. Therefore, it was tested briefly. Table 7.5 presents some results. The two columns to the left below the

6 For real numbers represented by the data type *Extended* (precision: 19 to 20 decimals), the simulation uses the function *Ran1* by Press and associates [89:219] and for real numbers represented by the data type *Real* (precision 7 to 8 decimals) the module *Ran3* by Press et al. [89:221-2]. Both generators produce uniformly distributed random numbers in the interval [0, 1).

headings *"mean"* and *"standard deviation"* relate to 100 tests each containing 1,000 random numbers. The mean of these numbers deviates at most 0.0835 from 0. For tests holding 10,000 numbers, the maximum deviation drops to 0.0301. The standard deviation of the means reveals, that in some 69% of the tests with 1,000 numbers the mean deviates less than 0.0322 from 0. For 73% of the larger tests, this deviation equals 0.0121[7]. The standard deviation per test reveals a similar pattern. The spread of the standard deviations falls sharply, if the number of test elements increases from 1,000 to 10,000.

	Number of tests : 100			
	Mean		Standard deviation	
Number of elements	1000	10000	1000	10000
Minimum	-0.0835136	-0.0301332	0.9403171	0.9788876
Maximum	0.0677326	0.0289006	1.0531324	1.0285429
Mean	0.0006936	-0.0012130	0.9992844	1.0002390
Standard deviation	0.0315462	0.0109593	0.0213972	0.0076874

Table 7.5 - Random number sets drawn from the standard normal distribution

In the simulation, each cohort initially holds 10,000 men or women. The results in table 7.5 suggest, that this cohort size creates favourable conditions for generating a set of x's that truly reflects the prevalence as determined by epidemiologic findings plus the approximation method presented in section 7.2. Nonetheless, these value assignments are not legitimate. The random numbers z, that determine the x's through y's, are drawn incoherently. Consequently, the *peripheral retina* might accidentally receive a particularly favourable value, while the *peripheral vision* of the same eye receives a lamentable value. This is contrary to the dependence of the second retinal aspect upon the first.

To generate cohesion, the value assignments respect the structure represented by figure 7.6 for every patient individually. The eight rectangles on the last two lines represent the four retinal aspects of the left and the right eye. As the human body forms an entity, the disease progression in both eyes is related to the general health condition of that particular patient. Similarly, it seems justifiable, that the various retinal aspects of

(continued)

Random numbers from normal distributions are determined by the algorithm of Box, Miller and Marsaglia on the basis of uniform random numbers [Press 89:225-6; Rugg 89:97].

7 These rounded numbers refer to the absolute value of the mean of the averages plus the standard deviation of the averages.

one specific eye are correlated to each other. Finally, the *central acuity* depends on the condition of the *macula*, while the *peripheral vision* is related to the state of the *peripheral retina*.

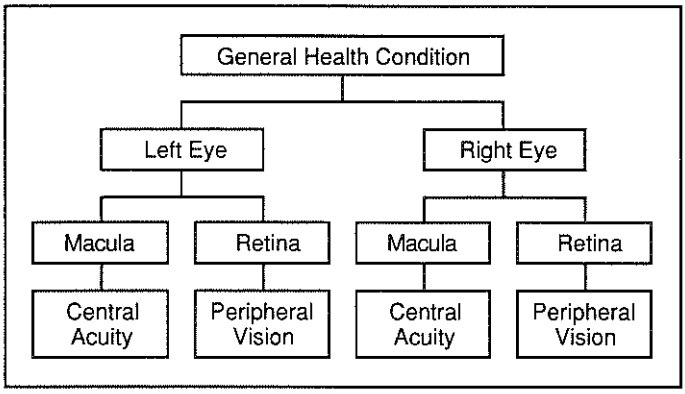

Figure 7.6 - Links of value assignments per patient

Respecting these relationships implies, that the initial random numbers for the eight retinal aspects per patient may only differ within some margins. Therefore, the simulation generates additional random numbers for every patient individually. For both the left and the right eye, a random number is drawn from the standard normal distribution: z_L and z_R. The first number, z_L, indicates the general health condition. The second number, z_R, may deviate from z_L by less than 0.25 (cf. 7.13 a). After drawing z_L, the computer executes a *repeat...until* instruction to generate a random number, until an acceptable value of z_R is drawn. Thus, z_L is the anchor value. The inequalities 7.13 b to 7.13 i mention the conditions governing how the z-values of the eight retinal aspects are determined successively. In each inequality, the first z forms the anchor value.

$$|z_L - z_R| < 0.25 \qquad (7.13\ a)$$

$$|z_L - z_{Macula_L}| < 0.25 \qquad |z_R - z_{Macula_R}| < 0.25 \qquad (7.13\ b,c)$$

$$|z_L - z_{Retina_L}| < 0.25 \qquad |z_R - z_{Retina_R}| < 0.25 \qquad (7.13\ d,e)$$

$$|z_{Macula_L} - z_{CentralAcuity_L}| < 0.25 \qquad |z_{Macula_R} - z_{CentralAcuity_R}| < 0.25 \qquad (7.13\ f,g)$$

$$|z_{Retina_L} - z_{PeripheralVision_L}| < 0.25 \qquad |z_{Retina_R} - z_{PeripheralVision_R}| < 0.25 \qquad (7.13\ h,i)$$

In all these nine inequalities, 0.25 is the upper limit. This number is chosen arbitrarily from sheer necessity, because the available evidence does not provide adequate directions. However, the simulation may handle other upper limits. It can also use different limits per retinal aspect or per eye. After these constrained initial value assignments, the cohort embodies stronger and weaker patients, regarding the condition of the retina. Despite this refinement, the set of values of each retinal aspect still reflects the actual prevalence close to truly. The size of the cohort favours this. However, even if the initial value assignments would cause a shift from the actual prevalence, this will not really obstruct the simulation. The prevalence of DR and visual impairment is initially nearly negligible. Therefore, most of the weakest patients then suffer neither from DR nor from visual impairment, as illustrated by figure 7.4 in the previous section. Apparently, the retinal condition in the cohort then has a rather limited spread near the upper bound. Furthermore, once every three months, value assignments reconcile the distribution of the condition of each retinal aspect with the actual prevalence for that period. This method will now be described.

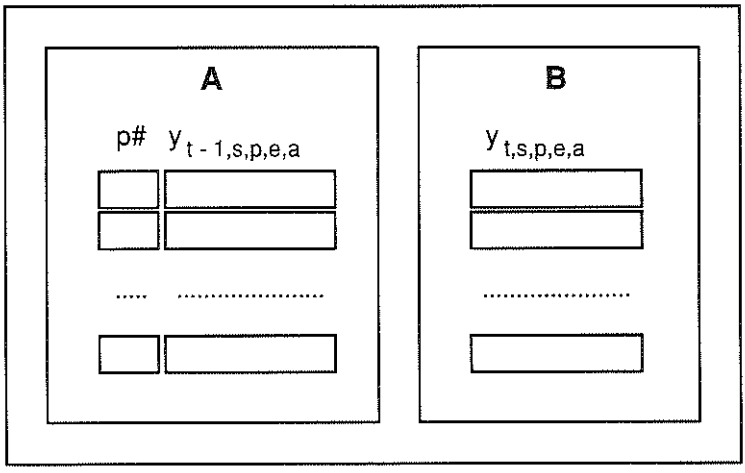

Figure 7.7 - Value assignment without order alteration

For each gender, each eye and each retinal aspect separately, the values of the previous period t−1 are stored in array A. This array might at one particular moment hold the values representing the condition of the peripheral retina in the left eye of all living masculine patients. Figure 7.7 presents array A schematically as an $n \times 2$ matrix that contains two numbers per patient for n patients: the patient number p# and the condition y of the retinal aspect. The first column of A mentions y-values instead of x-values, because it is technically more effective to express the condition in the interval $(-\infty, +\infty)$. The rows of A are sorted in ascending order on y.

Array B, forming an n row vector, accepts n random numbers drawn from the normal distribution ($\mu_{t,a}$, $\sigma_{t,a}$). Although the simulation uses sophisticated random number generators, it nevertheless compares the mean μ_B and the standard deviation σ_B of these n random numbers to $\mu_{t,a}$ and $\sigma_{t,a}$ respectively. If the differences are unacceptable[8], array B receives n new random numbers. Once array B holds an acceptable set, its elements are sorted in ascending order. Then for all acceptable j's, the value of element b_j in array B is assigned to the patient whose number is indicated by element $a_{j,1}$ of array A $\{j \in \mathbf{Z}^+ \mid j \leq n\}$. Element b_j therefore holds the new value of the retinal aspect: $y_{t,s,p,e,a}$.

This assignment method enables tracing diabetic patients individually per eye and per retinal aspect. Furthermore in every period, the set of values assigned to a specific retinal aspect corresponds to the prevalence of DR or visual impairment. Nonetheless, this method suffers from a serious drawback. It does not permit the disease progression of an individual patient to deviate from the general trend. Figure 7.7 may help to understand this point. The patient whose data appear after sorting on row 1 of array A, has the poorest condition of the specific retinal aspect in period t–1. In period t, the same patient receives the lowest value in array B. Similarly for every retinal aspect, each patient gets a new value, that confirms the previously established cohort order. Patients with a poorer condition remain comparatively weak until the end of the simulation, whereas an initially better state guarantees a permanently stronger condition. This course of events is not quite realistic.

The easiest solution to this problem is assigning the values of array B at random to all living patients, provided each value in B is assigned only once. Although the disease progression in the whole cohort then harmonises with the empirically observed prevalence, this solution is far from acceptable. It raises objections, like the ones discussed before, because the condition of a retinal aspect can fluctuate at random within the prevailing distribution. This may cause extreme and unrealistic shifts. A blind patient might for instance receive a value that corresponds to good vision in the following period. Because DR and blindness are irreversible disorders, this solution alienates the simulation from reality.

If the individual progression deviates from the general trend within narrow limits only, both objections can be met. For that reason, array A in figure 7.8 includes four extra columns. Again, the columns p# and $y_{t-1,s,p,e,a}$ receive the patient numbers and the

8 The set of random numbers in array B is acceptable, if $|\mu_B - \mu_{t,a}| < 0.05\ \sigma_{t,a}$ and $|\sigma_B - \sigma_{t,a}| < 0.05\ \log_{10}(\sigma_{t,a} + 1.01)$.

individual values of some retinal aspect in the previous period. The rows of array A are sorted in ascending order by the values of the retinal aspect y in column 2. The computer then assigns the number R# *(reference number)* to each element of the third column. This number equals the row number after sorting.

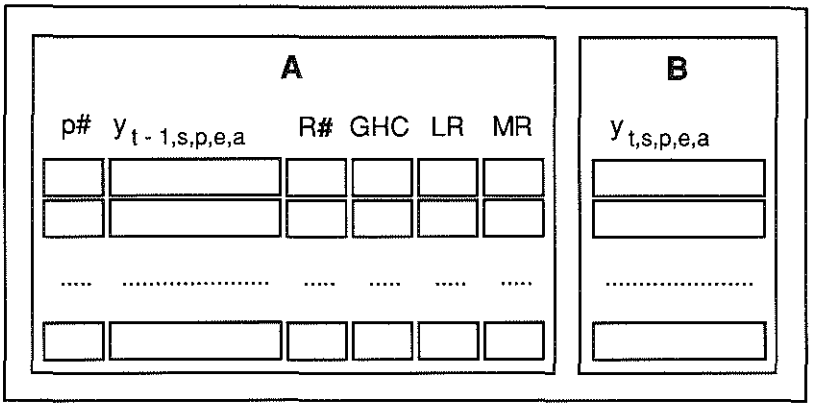

Figure 7.8 - Value assignment with order alteration

Let us now presume, that in period t 10,000 patients are alive, while the maximum freedom of movement equals 1%. This means, that the individual rank in period t may differ at most by 100 from the rank in period t−1. For that purpose, uniformly distributed random numbers r $\{r \in \mathbf{R} \mid 0 \leq r \leq 100\}$ are assigned to the cells of column GHC *(General Health Condition)*. Numbers smaller than 50 indicate a relative worsening of the individual condition as compared to the general disease progression in the cohort. The opposite holds for numbers greater than 50. Besides column GHC, column R# contains a strictly monotonously increasing set of integers ranging from 1 to 10,000. The rows of array A are now sorted in ascending order on the sum of the row elements R# and GHC. A row may alter its rank by 100 or less in that process. Then, for all acceptable j's, the value of element b_j in array B is assigned to the patient whose number is indicated by element $a_{j,1}$ of array A $\{j \in \mathbf{Z}^+ \mid j \leq 10{,}000\}$. The rank of a patient's retinal aspect may then change by 100 or less.

This method allows patients to deviate individually from the general disease progression, while the cohort as a whole respects the observed prevalence. In the previous example, the maximum deviation may seem rather small. Ultimately however, these smaller deviations may result in rather large cumulative deviations, as all retinal aspects receive a new value once per period. IDDM-patients, for instance, are followed on average for over 40 years, so that they may alter their position more than 160 times.

Array A also contains the columns LR *(left-right)* and MR *(macula-retina)*. They enable refining the value assignments according to the explanation of figure 7.6. In each period and for every patient, one random number is assigned to GHC, two numbers to LR and four numbers to MR. The rows of array A are then sorted in ascending order on the sum of the four row elements R#, GHC, LR, and MR. The random number GHC sees to all value assignments related to one patient and one period. The first random number LR jointly determines the four value assignments of the left eye, the second random number LR the right eye. Finally, each random number MR takes care of two value assignments per eye: (1) macula or peripheral retina and respectively (2) central acuity or peripheral vision.

A rather high GHC value reflects a relatively favourable development of the patient's general health condition during a specific period. As the element GHC is part of the sorting key in all individual value assignments, a comparatively high value improves the patient's chances eight times. Similarly, a relatively high random number LR favours all the four value assignments related to one eye. Finally, a rather high random number MR makes it more likely, that either the macula and the central acuity or the peripheral retina and the peripheral vision both receive comparatively auspicious new values. Vice versa, in all instances, the same reasoning bears upon comparatively low random numbers. This method promotes the cohesion of value assignments related to (1) a particular patient, (2) a particular eye, and (3) two affiliated retinal aspects. Furthermore, it allows each patient to follow an individual path, while the disease progression in the cohort as a whole complies with epidemiologic findings.

This solution also offers technical advantages. The values determined for the cohort as a whole in period t are independent of the values in previous periods. Hence, potential deviations in the past cannot cause disturbances in the future. Not all models provide this degree of stability. When systems of linear or non-linear equations are solved iteratively, "explosions" may occur. That is to say, the values of the unknown variables drift further and further away from their equilibrium values, as the number or iterations increases. Such explosions may provoke serious problems, the more so because mathematics provides few instruments to discover in advance, whether an iterative solution converges or not. This applies even to well-known solution techniques, like the Gauss-Seidel method [Hughes-Hallett 79a, 79b; Crijns 85:89-94].

On the other hand, this solution has drawbacks. There are, above all, no epidemiologic findings to support the choice of the upper limits of the random numbers in the columns GHC, LR, and MR of array A. Nonetheless, it would be fundamentally incorrect to ignore the coherence that characterises the progression of various retinal as-

pects in one eye or one patient [Klein 84e; Moss 88; Chantelau 89]. This forces the simulation to recourse to assumptions. Arbitrarily, the maximum rank shift per period is fixed at 0.25% of the number of living patients. The results presented in part C and part D enable the reader to assess personally, whether this upper limit is realistic. Anyhow, the simulation accepts each upper limit from 0% to 100% as well as variations in the course of time. At the start of the simulation, the upper limit could be rather high. Later, it might gradually decrease. This would imply, that the distinction between healthier and weaker patients sharpens, as the simulation advances.

The room for individual disease progression may create problems near the border between *moderate vision* and *blindness*. After a small upward shift, the retinal aspect *central acuity* may move from the upper region of the category *blindness* to the lower segment in the category *moderate vision*. The simulation solves this problem rather straightforwardly by only allowing one-way traffic across this border while forbidding movements from *blindness* to *moderate vision*. However, this simple solution creates a new problem. It is no longer possible to assign all the values of array B to the cohort (cf. figure 7.8). Consequently, the disease progression in the cohort may deviate from the observed progression.

Tests demonstrate however, that this easy solution does not affect the results appreciably. There may be three explanations for this result. First, the random numbers GHC, LR, and MR have a rather low upper limit. Border crossings in the wrong direction therefore cover small distances. Their forbidding hardly affects the mean and the standard deviation in the cohort as a whole. Second, the simulation automatically creates a countervailing force. As more crossings have been forbidden, the remaining patients in the category *moderate vision* receive on average more favourable random numbers and the traffic from *moderate vision* to *blindness* falls. Third, the prevalence of blindness increases eventually. If the traffic between *moderate vision* and *blindness* were completely free, most movements across the border would be from the first to the second category.

As this solution alters the results only insignificantly, the simulation model has no balancing procedures. However, such modules could be implemented quite easily. This issue is passed over, as it is of secondary importance. On the other hand, the simulation allows regression from PDR to BR, or from ME to BR. According to the findings of Beetham [63] and Hendrikse [90:11], regression is confined to 4% of the patients concerned.

Finally, the simulation encounters a purely technical problem. The value assignments to each retinal aspect require several sorting processes, that are quite time-consuming. The author reduced the sorting time of the fastest algorithm found in publications on computer programming, *Quick Sort* [Wirth 76:56-87; Press 89:254-69], by 25% to 50%[9]. Nevertheless, the simulation requires nearly seven days of computer processing for 2 × 10,000 IDDM-patients and five scenarios (Apple Macintosh, Motorola 68030 plus mathematical coprocessor 68882, 16 MHz). As such, this causes no difficulties. However, the processing time is an obstacle to sensitivity analyses, especially for NIDDM-patients. As part D will explain, they call for six different simulations requiring over a month computer processing.

7.7 Concluding Remarks

The simulation starts from epidemiologic data in medical publications on the prevalence of DR and subsequent visual impairment. This data set does not suffice to observe four retinal aspects in each patient's eye separately. So, the simulation has recourse to approximation methods and assumptions for filling these gaps. Although the base is rather limited, the previously mentioned methods enable the simulation to generate a large number of data on the individual disease progression. Some 25.6 million[10] values are produced on the condition of retinal aspects, if the simulation observes 2 × 10,000 patients for forty years on average with four value assignments per year. Consequently, figure 7.9 gives a feeble impression of the expansion in the original data set.

These methods are not void of pitfalls. In the inversed data pyramid, the position of the downward oriented top determines the position of the base situated above. Minor changes of epidemiologic data may affect the derived data considerably. Therefore, gathering epidemiologic evidence does not suffice. Some understanding of the pathogenesis of DM and DR is also required to filter the evidence where needed and to choose adequate assumptions. Obviously, this understanding does not guarantee correct hypotheses.

9 The time gain depends on the initial ordering of the array. The smallest gain relates to disordered arrays, the largest to ordered arrays. The simulation handles both fully unordered and nearly ordered arrays. On average, the time gain should be at least 30%.

10 2 × 10,000 × 40 × 4 × 2 × 4 = 25,600,000

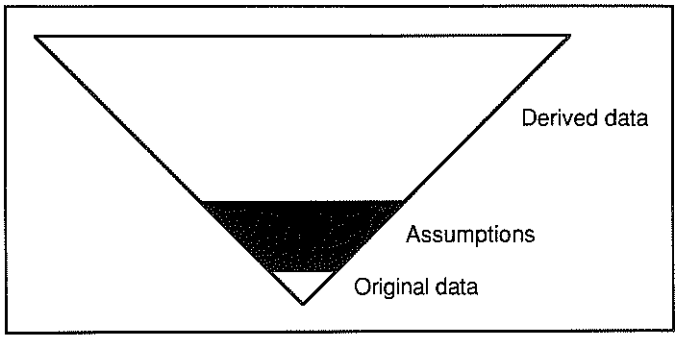

Figure 7.9 - Data pyramid

Nevertheless, these methods constitute quite a challenge. More than other simulation techniques, they enable imitating the individual disease progression of a larger number of patients over a longer period, while distinguishing several retinal aspects. The disease condition is recorded on a scale that is continuous, seen from the perspective of the objectives in this study. Moreover, the different retinal aspects of one patient develop coherently. Finally, the individual health condition is positively related to the condition in previous periods. This distinguishes the simulation from the Markov-technique presented in chapter 4, where the state in period t is only associated with the condition in period t–1 and not with previous periods.

After this analysis of the simulation methods, the next chapter presents the simulation structure.

8

Structure

8.1 Introduction

The computer programme has a modular structure. The modules may be divided into two categories. The first accommodates auxiliary modules, like random number generators, functions for logistic transformations and sorting procedures. These modules can support various other programmes. As they are examined extensively in publications on computer algorithms, they are not presented in this manuscript [e.g. Wirth 76; Knuth 81; Syslo 83; Press 89; Rugg 89].

The second category holds modules that were written quite specifically for this simulation. They are not examined elsewhere, because of their particular nature. For the sake of justification, this chapter presents the general lines of these modules, while omitting technical details. These modules have an executive or a co-ordinating mission. Executive modules imitate some aspects of ophthalmic processes, such as eye examinations, fluorescein angiograms and laser treatments. Some of them determine the individual progression of DR and the date of death, by epidemiologic data. Co-ordinating modules activate other modules in a specific sequence. To illustrate this, figure 8.1 presents the umbrella module *Simulation*. After the execution of the module *Initialisation*, it enables cohorts of diabetic patients to complete S+1 scenarios through unconditional iterative calls of the module *Scenario*, where s consecutively equals one of the numbers 0, 1, ... S $\{S \in \mathbf{N}\}$. The module *Conclusion* ends the simulation.

Figure 8.1 discloses, that the module *Scenario* co-ordinates the processing of a specific scenario. During initialisation, the parameter s determines the frequency of eye examinations. Then, the module *Year* is called Y times with the parameter y $\{y = 1, 2, ... Y; Y \in \mathbf{Z}^+\}$. Y equals the number of the year, when the last patient passes away. Obviously, the value of Y is conditional on the mortality in the cohort. For all patients, the onset of DM coincides with the beginning of year 1. The module *Year* activates the

module *Term* with the parameter t {t = 1, 2, ... T; T ∈ $\mathbf{Z}^+$}. The value of T is arbitrarily chosen before the start of the simulation. Finally, the module *Term* successively calls the modules *Disease progression*, *Mortality*, and *Screening & Treatment*.

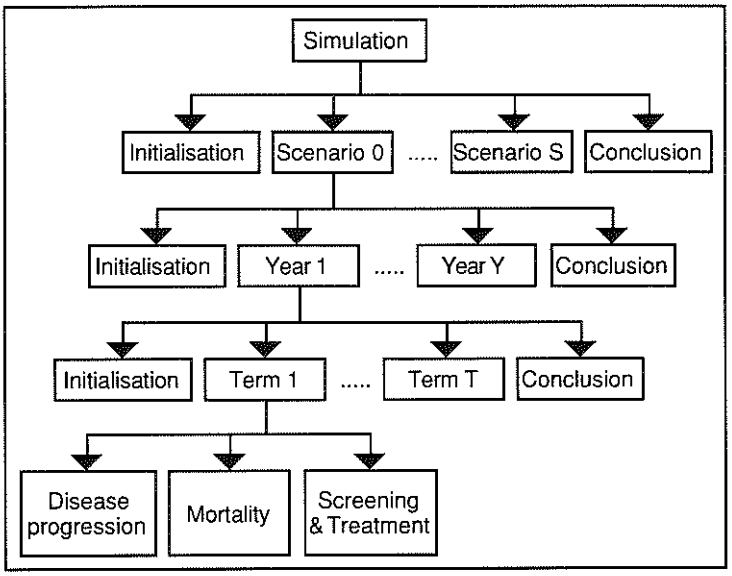

Figure 8.1 - Modular structure of the simulation

For the sake of clarity, figure 8.1 indicates at each level just one call to the lower level. The next sections analyse the modules pictured in figure 8.1 with charts closely related to *Action Diagrams* [Martin 88:245-73].

8.2 Simulation

In this context, the name *Simulation* relates to the imitated progression of retinal conditions in a cohort of diabetic patients. It starts at the onset of DM and ends in the year, when the last cohort member deceases. Initially, a cohort holds 10,000 female and 10,000 male patients. It is homogeneous concerning the type of DM and the age of onset. There is one simulation for IDDM, where every patient faces IDDM from the age of fifteen. Furthermore, there are six simulations for NIDDM: three for NIDDM-a and three for NIDDM-b. These three simulations represent three ages of onset: 35, 55, and 75 years.

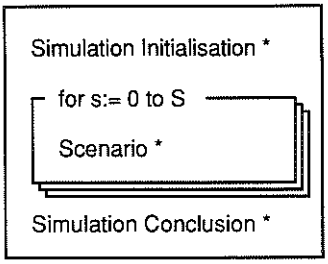

Figure 8.2 - The module *Simulation*

Figure 8.2 presents the module *Simulation*. After initialisation, the module *Scenario* is called iteratively S+1 times. Finally, the module *Simulation Conclusion* ends the simulation. The asterisks indicate modules, that a subsequent section investigates more closely.

8.3 Simulation Initialisation

As indicated in figure 8.3, this module allocates random access memory in the computer to some arrays, that may be compared to vectors and matrices in linear algebra. These arrays store: (1) general findings on mortality and the prevalence of DR, blindness, and moderate vision, (2) individual data, and (3) auxiliary variables.

Memory allocation to arrays storing :
- hazard rates
- means and standard deviations of normal distributions representing the prevalence of DR and visual impairment
- personal data of diabetic patients in the cohort
- auxiliary variables

Reading (from file) and storing hazard rates of the general population

Calculating and storing hazard rates corresponding to the severity of DR and visual impairment

Calculating and storing means and standard deviations of normal distributions representing the prevalence of DR and visual impairment

Calculating and storing auxiliary variables

Figure 8.3 - The module *Simulation Initialisation*

Then, the computer reads a file containing the average hazard rates of the general population in the Netherlands during the years 1983-1987. These rates, based on findings

by the Dutch *Central Bureau of Statistics* [CBS 88b[1]], are classified by gender and age (0.0, 0.5, 1.5, 2.5, ... 109.5 years). The data is stored in an array like matrix 8.1. The elements $\lambda_{F,1}(0.0)$, $\lambda_{F,1}(0.5)$, ..., $\lambda_{F,1}(109.5)$ represent the hazard rates of women in the general population, whereas the elements $\lambda_{M,1}(0.0)$, $\lambda_{M,1}(0.5)$, ..., $\lambda_{M,1}(109.5)$ relate to men in the general population. Footnote 1 in section 4.2 defines the hazard rate. Apparently, not one person reaches the age of 110.5 years. Therefore, $\lambda_{\ldots,\ldots}(109.5)$ equals 1.

$$\begin{bmatrix} \lambda_{F,1}(0.0) & \lambda_{F,0.95}(0.0) & \ldots & \lambda_{F,0.3}(0.0) & \lambda_{M,1}(0.0) & \lambda_{M,0.95}(0.0) & \ldots & \lambda_{M,0.3}(0.0) \\ \lambda_{F,1}(0.5) & \lambda_{F,0.95}(0.5) & \ldots & \lambda_{F,0.3}(0.5) & \lambda_{M,1}(0.5) & \lambda_{M,0.95}(0.5) & \ldots & \lambda_{M,0.3}(0.5) \\ \lambda_{F,1}(1.5) & \lambda_{F,0.95}(1.5) & \ldots & \lambda_{F,0.3}(1.5) & \lambda_{M,1}(1.5) & \lambda_{M,0.95}(1.5) & \ldots & \lambda_{M,0.3}(1.5) \\ \lambda_{F,1}(2.5) & \lambda_{F,0.95}(2.5) & \ldots & \lambda_{F,0.3}(2.5) & \lambda_{M,1}(2.5) & \lambda_{M,0.95}(2.5) & \ldots & \lambda_{M,0.3}(2.5) \\ \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\ \lambda_{F,1}(109.5) & \lambda_{F,0.95}(109.5) & \ldots & \lambda_{F,0.3}(109.5) & \lambda_{M,1}(109.5) & \lambda_{M,0.95}(109.5) & \ldots & \lambda_{M,0.3}(109.5) \end{bmatrix} \quad (8.1)$$

These rates do not suffice however, as DM impairs the expectation of life. For that reason, matrix 8.1 contains, both for women and for men, another 14 columns. They represent respectively 0.95, 0.9, 0.85 ... 0.3 times the life expectation of the general population. Several studies reveal, that the reduction of life expectation depends on the age of onset of DM. As DM occurs at a younger age, the absolute fall in life expectation increases. However, the relative reduction of life expectation at the age of onset of DM is on average approximately the same for all groups of diabetic patients [Marks 71; Goodkin 75; Davis 79; Dorman 82, 84; Knatterud 83; Borch-Johnsen 86; Panzram 87; Parving 88; Veen 88; DERIMSG 91a, 91b]. What implies a relative fall by one third, for example? If the expectation of life for the general population equals 60 years at the age of 15, then diabetic patients will live on average another 40 years after DM occurs at the age of 15. Persons developing DM at the age of 50 will live thereafter 20 years on average, in case the general population has a life expectation of 30 years at the age of 50.

How are the elements $\lambda_{F,0.95}(0.0)$ ... $\lambda_{F,0.3}(109.5)$ and $\lambda_{M,0.95}(0.0)$ ... $\lambda_{M,0.3}(109.5)$ determined? For ages up to the age of onset of DM, the hazard rates

1 The life expectation of the general population at the age of 14.5 years rose by 0.20 years for women and by 0.37 years for men in the period 1986-1990 as compared to 1983-1987. If diabetic patients have two thirds of the life expectation of the general population at the onset of DM, this implies an average increase of 0.19 years, or 0.45%, for IDDM-patients [CBS 88b, 91a].

equal the hazard rates of the general population. To older ages, the transformation formula 8.2 applies.

$$\lambda_{s,r}(g) = [\lambda_{s,1}(g)]^m \tag{8.2}$$

$\{s \in \{F,M\};\ r \in \{0.3,\ 0.35,...0.95\};\ g \in \{0.0,\ 0.5,\ 1.5,...109.5\};\ m \in \mathbf{R} \mid m \geq 0\}$

The symbol s represents the variable *gender*, r the *relative expectation of life* and g the *age*. For all elements in one particular column, one value of factor m is valid. At this value, equation 8.3 is approximately[2] true. Let us first examine equation 8.3. Subsequently, we will consider how factor m is determined.

$$r = \frac{0.5 + \sum_{g=i}^{\infty} \prod_{b=i}^{g} [1 - \lambda_{s,r}(b)]}{0.5 + \sum_{g=i}^{\infty} \prod_{b=i}^{g} [1 - \lambda_{s,1}(b)]} \tag{8.3}$$

The symbol i indicates the age of onset of DM, whereas b represents an auxiliary variable $\{b,i \in \mathbf{N}\}$. The numerator of the fraction determines the life expectation of diabetic patients at the onset of DM by the upward adjusted hazard rates $\lambda_{s,r}(b)$. The denominator calculates the life expectation of the general population at the same age by the "normal" hazard rates $\lambda_{s,1}(b)$. As the numerator and the denominator have the same structure, the further examination of equation 8.3 concentrates upon the numerator.

$$F_{i,s,r}(g+1) = \prod_{b=i}^{g} [1 - \lambda_{s,r}(b)] \tag{8.4}$$

Equation 8.4 presents the product term of the numerator. It indicates the fraction survivors $F_{i,s,r}(g+1)$. This fraction is the quotient of (1) the number of patients of gender s and relative expectation of life r who are alive at the age of g+1 years, or g–i+1 years after the onset of DM, and (2) the number of patients who were alive at the onset of DM $\{g \geq i;\ F_{i,s,r}(g+1) \in \mathbf{R} \mid 0 \leq F_{i,s,r}(g+1) < 1\}$.

$$R_{i,s,r}(i) = \sum_{g=i}^{\infty} \frac{F_{i,s,r}(g) + F_{i,s,r}(g+1)}{2} \tag{8.5}$$

2 The approximation meets the inequality: $|r_a - r| < 10^{-5}$ (r_a : approximated value of r).

Equation 8.5 indicates the absolute expectation of life $R_{i,s,r}(i)$ at age i for gender s and the relative expectation of life r, if the incidence of DM occurs at age i. As $F_{i,s,r}(i) = 1$, equation 8.5 simplifies to equation 8.6.

$$R_{i,s,r}(i) = 0.5 + \sum_{g=i}^{\infty} F_{i,s,r}(g+1) \qquad (8.6)$$

Equation 8.6 assures that the right term of equation 8.3 equals the quotient of the expectation of life based respectively on upward adjusted hazard rates and on "normal" hazard rates. How is factor m determined for specific values of s and r? Algebraically, formula 8.2 may be substituted in equation 8.3. The equation is then rearranged, so that factor m appears on the left side. If this solution is feasible, it requires solving a complex equation. The following numerical solution avoids these problems.

(1) $m = 0.5$ (LowerLimit + UpperLimit)
(2) Determine the hazard rates $\lambda_{s,r}(g)$ in the numerator of equation 8.3 by substituting in formula 8.2 the value of m determined in phase (1).
(3) Determine the value of the right term in equation 8.3 and name it r_a.
(4) Determine the absolute difference of r and r_a.
(5) If the difference found in phase (4) is smaller than the precision margin, which the simulation arbitrarily sets to 10^{-5}, then go to phase (8).
(6) If $r < r_a$ then UpperLimit becomes: 0.5 (LowerLimit + UpperLimit), otherwise LowerLimit becomes: 0.5 (LowerLimit + UpperLimit).
(7) Return to phase (1).
(8) The value of m determined in phase (1) offers an acceptable approximation of the relative life expectation. (end of algorithm)

Formula 8.2 discloses, that $\lambda_{s,r}(g)$ is a strictly monotonously decreasing function of m $\{m \geq 0\}$ for any value of $\lambda_{s,1}(g)$ $\{0 \leq \lambda_{s,1}(g) \leq 1\}$, excluding the upper and lower limits. Consequently, $[1 - \lambda_{s,r}(g)]$, as well as $F_{i,s,r}(g)$ and $R_{i,s,r}(i)$, are strictly monotonously increasing functions of m. Moreover, $0 \leq m \leq 1$, as $r \leq 1$. If these prior conditions are met, it is possible to determine m approximately by recursive calls of this algorithm, which is closely related to *search by bisection* [Flanders 84:59]. The algorithm is executed for every combination of s and r that the simulation requires. In each run, the variables LowerLimit and UpperLimit are set initially to 0 and 1 respectively.

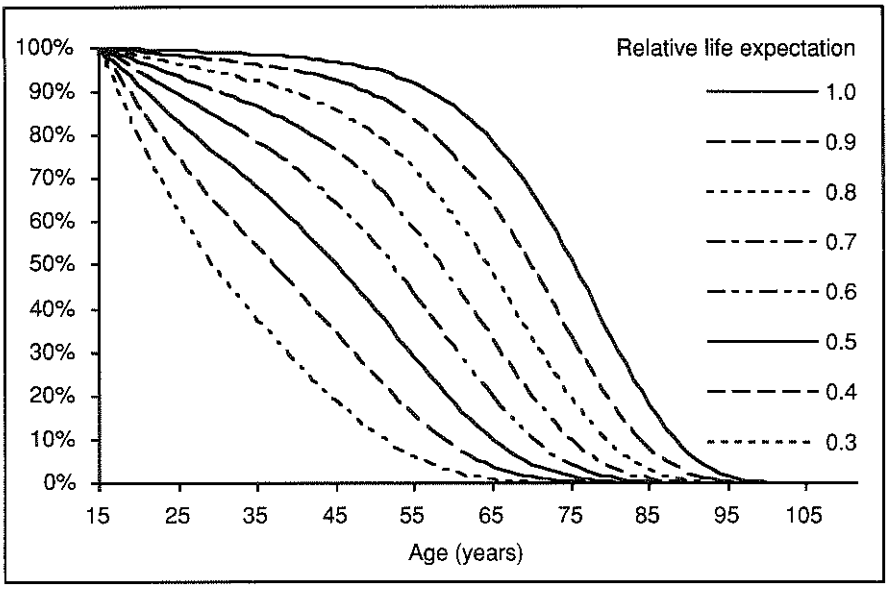

Figure 8.4 - Survivors fraction in cohorts of men who reached the age of 15 years

The hazard rates, assessed in phase (2) while executing the algorithm, are stored in matrix 8.1. Equation 8.4 indicates how these rates enable determining the survivors fraction $F_{i,s,r}(g)$. Figure 8.4 pictures the progression of this fraction for male patients who face DM from the age of 15 years. For reasons of clarity, the graph relates to a limited set of values for r: 0.3, 0.4, ... 1.0. The surface enclosed by the curve $r = 1.0$ and the two axes may be set to 1. Then, the similar surface below each curve equals r.

According to equation 8.2, the simulation resorts to exponential transformation for calculating vectors which represent various expectations of life. After transformation, all hazard rates have an acceptable value $\{0 \leq \lambda \leq 1\}$, provided $0 < m < 1$. This is a substantial asset. Besides, there are other transformation methods, like the *accelerated life* model. At age g, the survivors fraction in a cohort with a reduced expectation of life corresponds to the survivors fraction in the general population at age βg $\{\beta \in \mathbf{R} \mid \beta \geq 1\}$. This fraction relates to the number of live births. The *proportional hazards* model is another well-known transformation technique. The hazard rates of the general population are multiplied by factor γ $\{\gamma \in \mathbf{R} \mid \gamma \geq 1\}$ to determine the hazard rates of patients suffering from some disorder. Factor γ may be constant or age related. Alongside the *multiplicative proportional hazards* model, there is also the *additive* model. Finally, the transformation might follow the *transferred origin* model. A reduction of life expectation is reflected by a "jump" to hazard rates for higher ages [Kalbfleisch 80:119-62; Cox 84:64-75].

Considering the foregoing, this simulation model can be regarded as an *exponential hazards* model. In certain circumstances, the other models generate unacceptable values for λ, like $\lambda > 1$. Those models may also relate to values not to be found. The latter happens in the *transferred origin* model, when origin transferral causes the search of an age not mentioned in the life tables of the general population. These objections are not fundamental however, because it is usually sufficient to substitute $\lambda = 1$, if $\lambda > 1$ or in case λ cannot be found. Therefore, any model mentioned above may be selected. At any rate, the evidence on mortality rates of diabetic patients does not provide sufficient support for making a choice by objective criteria.

After the determination of the hazard rates, the mean μ and the standard deviation σ are assessed for each normal distribution representing the prevalence of DR, ME, PDR, moderate vision and blindness in the interval $(-\infty, +\infty)$. These calculations observe the guidelines put forward in section 7.4. Thereby, some problems emerge. The calculation of μ and σ is based upon y_1, y_2, $\Phi(y_1)$ and $\Phi(y_2)$. According to equation 7.8, y_1 and y_2 are the logit of respectively x_1 and x_2. The latter two symbolise the two upper limits for the retinal aspect at issue, indicated in table 7.4. For the interval $(-\infty, y_1)$ and $(-\infty, y_2)$ respectively, $\Phi(y_1)$ and $\Phi(y_2)$ represent the cumulative distribution of a normal distribution (μ, σ), formalised by equation 8.7.

$$\Phi(y_o) = \int_{-\infty}^{y_o} \frac{1}{\sigma\sqrt{2\pi}} e^{-0.5\left(\frac{y-\mu}{\sigma}\right)^2} dy \qquad (8.7)$$

According to equation 8.7, the four known variables may form a set of two equations with two unknown variables: μ and σ. For a normal distribution however, the integral of the probability density function cannot be determined algebraically [Abramowitz 72:931]. Fortunately, the probability density function is continuous. This enables numerical approximation, for instance with the Simpson rule [Press 89:117-24; Rugg 89:48-9].

A second problem appears, because $\Phi(y_o)$ is known, while μ and σ are unknown. However, each value of $\Phi(y_o)$ is related to one specific z-value, irrespective of the value of μ or σ. The standard normal distribution ($\mu = 0$; $\sigma = 1$) simplifies this problem. Its cumulative density function is a strictly monotonously increasing function of y. For that reason, the previously mentioned *search by bisection* method can help determining y_o by approximation starting from $\Phi(y_o)$. As the likelihood of extreme

z-values is negligibly small[3], the simulation uses the following start values: LowerLimit = −10 and UpperLimit = +10. They yield quite acceptable results. After deriving z_1 and z_2 from $\Phi(y_1)$ and $\Phi(y_2)$, μ and σ are determined by forming a set of equations like set 7.9.

8.4 Scenario

According to figure 8.5, the *Scenario Initialisation* is the first element of the module *Scenario*. It comprehends (1) opening output files for storing results, (2) initialising the screen to present the results, (3) determining the frequency of eye examinations, and (4) assigning initial values that express the individual retinal condition and visual acuity. The output files enable interchanging data between different types of software and processing the results more efficiently. A Pascal-programme, holding some 6,500 lines of code including comments, is the "engine" of the simulation. It exports the main results to text files. A spreadsheet imports these files. Then, it performs additional calculations, joins data from different files and recapitulates the main results in graphs and tables.

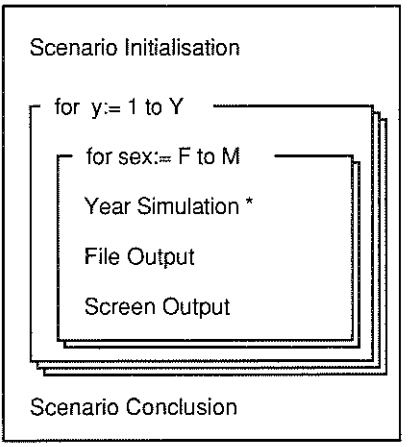

Figure 8.5 - The module *Scenario*

Table 8.1 specifies the frequency of eye examinations in five scenarios.

3 for instance: $P(|z| > 8) = 1.28 \times 10^{-15}$

Scenario	no DR	BR	ME and/or PDR
0	Never	Never	Never
1	Once every eight years	Once every four years	Once every two years
2	Once every four years	Once every two years	Once a year
3	Once every two years	Once a year	Twice a year
4	Once a year	Twice a year	Four times per year

Table 8.1 - Frequency of eye examinations in 5 scenarios

The simulation allocates one record per patient. Figure 8.6 presents its structure. Lowercase letters indicate data types: (b) boolean {true, false}, (d) diagnosed retinal condition {noDR, BR, ME, PDR, Blind}, (i) integer {−32,768 ... 32,767}, and (r) real $\{+/- 1.5 \times 10^{-45} \ldots 3.4 \times 10^{38}\}$. Curly braces enclose the range of the data types. The start of the simulation corresponds to zero, where dates are concerned. Dates are recorded by real numbers, so that specific moments during a year are indicated as fractions.

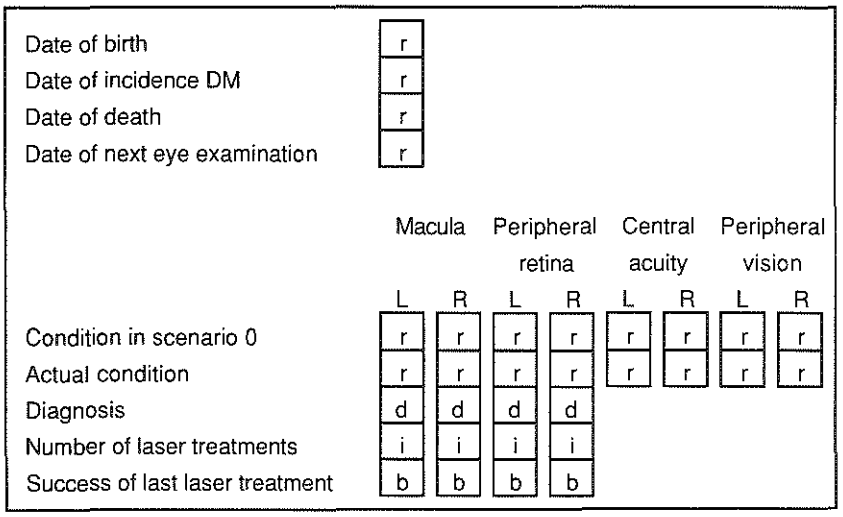

Figure 8.6 - Structure of a patient's record

The simulation simultaneously holds two separate data sets on the retinal condition and visual acuity. The first records the progression in the scenario without ophthalmic care,

the second in the scenario at issue. Both data sets require a substantial amount of memory[4]. Is it efficient to duplicate these rather large data sets?

The value assignment to retinal aspects in the module *Disease progression* is the key to the answer. After the explanation of the figures 7.7 and 7.8 in section 7.6, this method may be summarised as follows. The p living patients are ordered ascendingly according to the individual values of the retinal aspect at issue in the previous period. The general health condition, the eye condition and the condition of the affiliated retinal aspect may alter the order slightly. A normal distribution, with the parameters μ and σ reflecting epidemiologic evidence after transformation, constitutes the starting point for generating p random numbers. After ascending ordering, these p random numbers are assigned to the p patients according to their ordering, mentioned above. In other words, the random numbers depend solely on μ and σ, while the individual value assignments primarily relate to the individual values during the previous period.

This method appears to suit scenario 0 perfectly. In other scenarios however, value assignments after successful laser treatments provoke problems. As section 3.6 indicates, the model assumes, that the peripheral retina and peripheral vision stabilise after successful laser treatments of PDR. In case of ME, successful laser treatments halve the deterioration speed of the macula and central acuity. After non-successful treatments, retinal aspects continue their natural progression as if they never received laser treatment.

$$y^{c}_{t,s,p,e,a} = y^{0}_{t,s,p,e,a} \tag{8.8}$$

$$y^{c}_{t,s,p,e,a} = y^{c}_{t-1,s,p,e,a} \tag{8.9}$$

$$y^{c}_{t,s,p,e,a} = y^{c}_{t-1,s,p,e,a} + \frac{y^{0}_{t,s,p,e,a} - y^{0}_{t-1,s,p,e,a}}{2} \tag{8.10}$$

How does the computer model implement these assumptions? After non-successful laser treatments, retinal aspects traverse the module *Disease progression* - to be presented in section 8.6 - according to scenario 0. Equation 8.8 formalises this. The superscripts c and 0 indicate the scenarios c and 0 $\{c \in \{0, 1, 2, 3, 4\}\}$. After successful laser treatments, the value assignments regarding the peripheral retina and peripheral vision observe equation 8.9. The value assignments concerning the macula

4 The number of storage units - for the data type *real* and for $2 \times 10{,}000$ patients - equals per set: $2 \times 10{,}000 \times 4 \times 2 = 160{,}000$. If every storage unit of the type *real* holds four bytes, each set requires 640,000 bytes, or 625 kilobytes.

and central acuity follow equation 8.10. After successful treatments, the adjustment in scenario c equals half the change in scenario 0 [5]. Furthermore, equation 8.10 reveals why the retinal aspects, *macula* and *central acuity*, require statistics of scenario c and scenario 0.

According to equation 8.9, information on scenario 0 seems superfluous in describing the progression of the retinal aspects *peripheral retina* and *peripheral vision* in scenario c. To understand why this is false, let us presume that this information is absent in scenarios with ophthalmic care $\{c > 0\}$. Thanks to successful laser treatments, some patients improve their relative position in the cohort, while the relative position of other patients inevitably deteriorates. Value assignments largely depend on relative positions, as section 7.6 points out. Therefore, successful treatments affect value assignments through changes in relative positions. Paradoxically, successful treatments of some patients provoke less favourable value assignments for other patients. This conflicts with reality.

This substantial shortcoming can be remedied rather easily by simulating the disease progression in scenario 0 parallel to each scenario with ophthalmic care. The problems presented in the previous paragraph do not occur in scenario 0. In each period, the simulation model determines first the values for scenario 0. It then assesses the disease progression in scenario c $\{c > 0\}$ as follows. For retinal aspects that received unsuccessful laser treatment or no laser treatment, the value in scenario c equals the value in scenario 0, as indicated by equation 8.8. Value assignments after successful treatments comply with the equations 8.9 and 8.10. This solution may not appear efficient, as the computer has to imitate the disease progression in scenario 0 five times instead of once. That procedure requires some 75% of the total processing time for a cohort of $2 \times 10{,}000$ patients. However, this technique appears to offer the highest processing speed with today's desktop computers due to their memory constraints[6]. Moreover, this method enables to test the stability of the model by comparing the five runs of scenario 0 [7].

5 The computer model incorporates another refinement. In case of regression, the change in scenario c equals the mutation in scenario 0. For the sake of simplicity, the text disregards this refinement.

6 As mentioned before, the simulation follows IDDM patients from their fifteenth anniversary, when IDDM appears, until they pass away. On reaching the age of fifteen, the average expectation of life is nearly 42 years for male patients and approximately 46 years for female patients. A simulation covering 44 years while distinguishing 4 periods per year generates 1,408 data elements per patient for 4 retinal aspects per eye ($= 44 \times 4 \times 4 \times 2$), or 28,160,000 data elements for 20,000 patients. If the memory claim of the data type *real* equals 4 bytes, this corresponds to more

Figure 8.6 illustrates, that the data type d represents the diagnosis. It is a user defined data set collecting the following elements: *noDR*, *BR*, *PDR*, *ME* and *Blind*. Integer numbers indicate the number of laser treatments, while logical variables (type *boolean*) specify whether treatments were successful. Looking back on figure 8.5 reveals, that two nested iterative loops follow the initialisation procedure. The first loop relates to the years 1 to Y {$Y \in \mathbb{Z}^+$}, the second to gender F and M. After activating the module *Year Simulation*, presented in the next section, the simulation exports the main results to a file and to the screen. Once these two loops have been traversed, the module *Scenario Conclusion* ends the scenario. It disposes dynamic variables, accessed by handles, and reclaims internal memory space.

(continued)

than 107 megabytes (1 megabyte = $1{,}024^2$ bytes). The computer might however simulate the disease progression of female and male patients separately. Following 10,000 female patients requires some 56 megabytes {$\approx (46 \times 4 \times 4 \times 2 \times 10{,}000 \times 4) / 1{,}024^2$}. Besides, the simulation model holds other data. It would therefore be prudent to reserve at least 110 megabytes, or 60 megabytes in case of separate processing per gender. The random access memory of today's desktop computers does not yet meet this requirement. Hard disks might offer a solution to this problem, as they provide adequate space. In developing the simulation model, this solution was not investigated, because accessing data from a hard disk requires 1,000 to 10,000 times more time than from the random access memory.

7 During the design phase, the stability was tested as follows. The model completed twenty simulations, each representing 2 × 1,000 IDDM patients in 5 different scenarios. Every simulation generated for each scenario 50 data elements per gender per year from the onset of IDDM until the year when the last member of the cohort died. These data elements indicate, for instance, the number of survivors and the absolute prevalence of DR, ME, PDR, visual impairment and blindness. The twenty simulations included some 70 years. Consequently in each simulation and in each scenario, a vector of 70 elements was formed for each of the 50 variables. The twenty simulations generated twenty comparable vectors for each variable, each scenario, and each gender. The *Kolmogorov-Smirnov* test for two distribution functions analysed these twenty vectors in pairs. The test indicates, whether the two vectors belong to different distributions [Lindgren 76:487-91; Siegel 88:144-51; Press 89:518-22]. Twenty vectors require 190 (= 19 + 18 + ... + 1) two by two comparisons. Therefore, the total number of two by two comparisons equals 95,000 (= 190 × 2 × 5 × 50). In scenario 0, none of the 19,000 comparisons revealed significant differences. In each of the scenarios 1 to 4, significant differences emerged on average in 20 (0.1%) two by two comparisons. The average probability of each set of 190 two by two comparisons never revealed significant differences. Consequently, the results of the twenty simulations did not differ significantly and the model proves sufficiently stable for cohorts of 1,000 patients. As the stability of Monte Carlo simulations is positively correlated to the cohort size, the stability should be more than adequate in cohorts holding 10,000 patients.

8.5 Year Simulation

As illustrated in figure 8.7, this module includes two nested iterative loops. The first concerns the terms 1 to T {T ∈ $\mathbf{Z}^+$}, that divide each year into T equal parts. T always equals four in this investigation. The number of iterations P in the second loop corresponds to the number of living patients in the cohort at the end of the previous period.

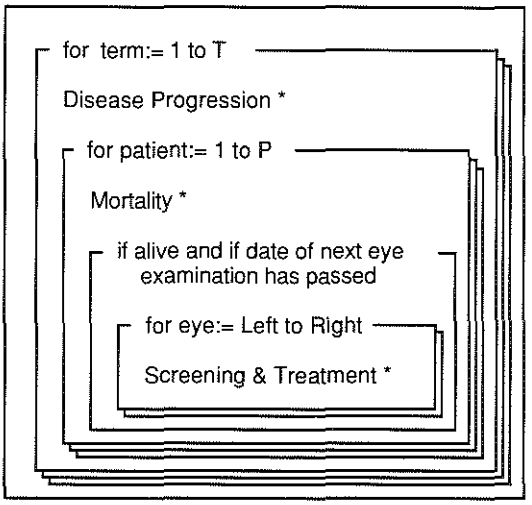

Figure 8.7 - The module *Year Simulation*

At the start of each term, *Year Simulation* activates *Disease Progression*. This module assigns new values to the retinal aspects of all living patients according to the technique presented in section 7.6. The next section shows, that the module *Disease Progression* has its own iterative structure for processing the disease progression of all living patients. Calling of this module once suffices to process the progression of all patients.

The module *Mortality* is an element of the second loop. It determines the hazard rate of one particular patient as a function of age, gender and severity of DR. Section 8.7 presents further details regarding this relationship. As the module *Disease Progression* is called before the module *Mortality*, the hazard rate during the term at issue depends on the health condition in the same term. By comparing the hazard rate with a random number, the module *Mortality* determines whether the patient stays alive. Ideally, the simulation model should accommodate to any moment of death. However, a patient who starts traversing the module *Screening & Treatment*, presented in section 8.8, cannot interrupt that process somewhere halfway, simply because the module offers no

provision for such interruption. The simulation model solves this problem straightforwardly. If a patient dies, the module *Mortality* generates another random number to determine whether death occurred at the beginning or at the end of the term. The odds of both moments are equal. The module *Screening & Treatment* may be traversed only in case the patient dies at the end of the term or later. Both eyes cross this module separately.

8.6 Disease Progression

Section 7.6 presents the essentials of this module. The present section therefore explains figure 8.8 only. First, the module generates a random number r_{GHC} for every living patient. This number indicates the individual general health condition. Then, there is an iterative loop concerning the left and the right eye. It generates P random numbers r_{LR} to typify the individual progression of the eye at issue. Within the iterative loop for the left and the right eye, there is another loop concerning the macula and the peripheral retina. It generates P random numbers r_{MR} representing the individual progression of both the central and peripheral retinal areas. In brief, seven random numbers are generated per patient: once r_{GHC}, twice r_{LR} and four times r_{MR} (cf. figure 7.6, section 7.6).

Then, there is another loop that successively relates to the macula or the peripheral retina plus the affiliated retinal aspect concerning vision. A brief explanation may suffice, because figure 7.8 in section 7.6 has illustrated this procedure already. For all living patients, the value of the retinal aspect at issue is stored in array A. The array is sorted on that value. Then, a reference number is assigned to each array element. The number represents to the array position of the array element after sorting. Array A is then sorted on the sum of the reference number and the three random numbers representing changes in the health condition. Patients may thus move to a neighbouring position in the order. Then, random numbers are drawn from a normal distribution that represents the prevalence of retinal disturbances of the retinal aspect at issue. After these values have been assigned to array B, the array is sorted. Finally, the order of patients in array A determines to which element of array D the new retinal values in array B are assigned. Array D contains the statistics of all patients stored in records according to the model presented in figure 8.6, section 8.4.

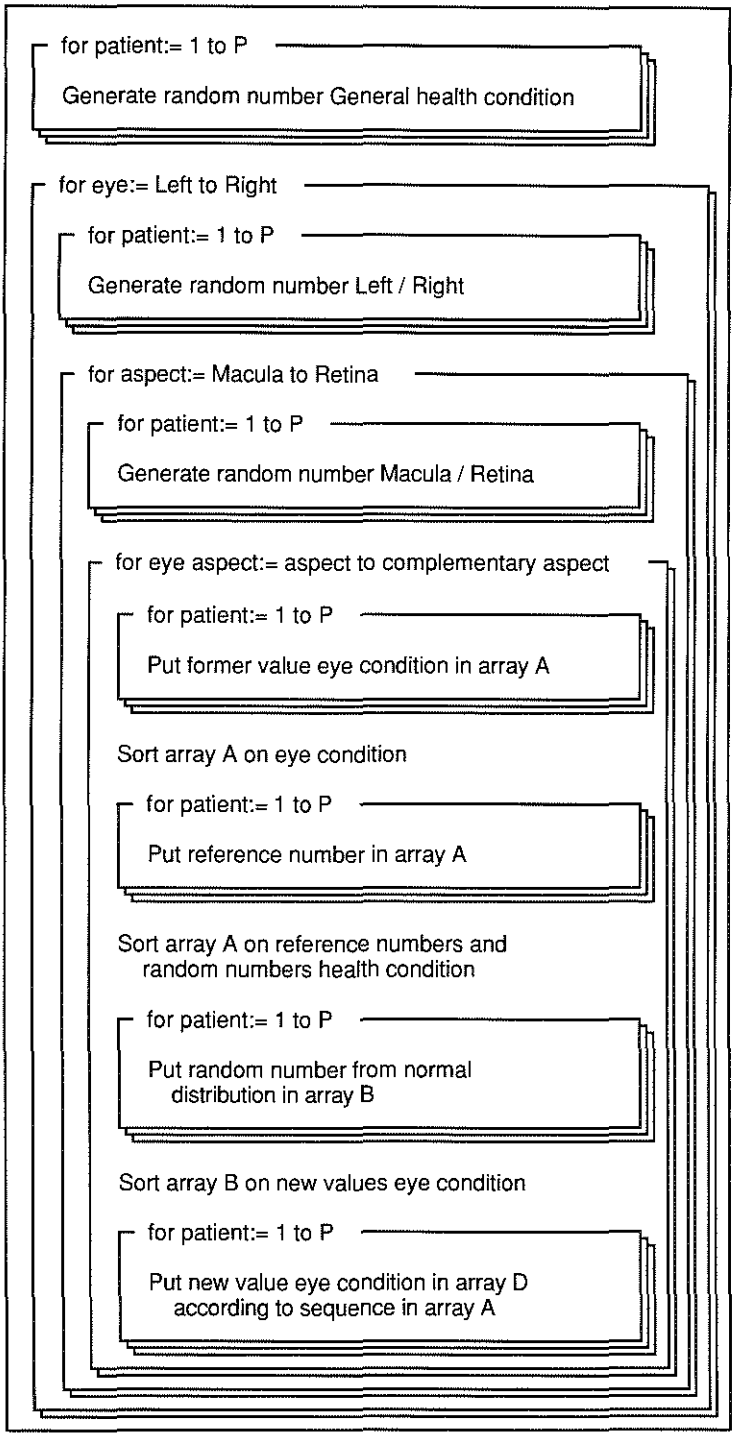

Figure 8.8
The module
Disease Progression

8.7 Mortality

Figure 8.9 presents the module *Mortality* schematically. All living patients traverse this module individually. After the individual hazard rate has been determined as a function of age, gender, and health condition, a random number r is drawn from a uniform distribution $\{r \in \mathbf{R} \mid 0 \leq r < 1\}$. If r is smaller than the hazard rate, the patient passes away and a second random number r is generated to determine, whether death occurred at the beginning or at the end of the term.

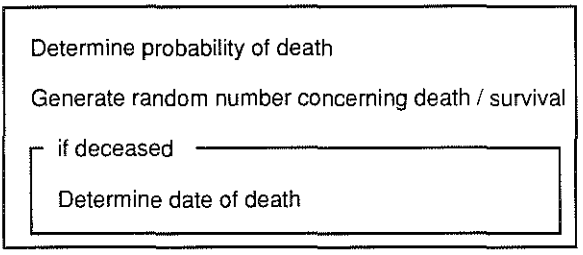

Figure 8.9 - The module *Mortality*

As section 8.3 indicates, the simulation holds 17 vectors per gender. The hazard rates in each vector represent a relative life expectation, that respectively equals 1, 0.95, 0.9, ... 0.3 times the life expectation of the general population in the Netherlands at the age of onset of DM. The module *Mortality* determines the individual hazard rate stepwise.

$$\xi_{t,s,p,e,a} = \rho_a + (1 - \rho_a)\, x_{t,s,p,e,a} \qquad \{\rho_a \in \mathbf{R} \mid 0 \leq \rho_a \leq 1\} \tag{8.11}$$

First, the health condition $x_{t,s,p,e,a}$ $\{x \in \mathbf{R} \mid 0 \leq x \leq 1\}$ in term t for gender s, patient p, eye e, and retinal aspect a is converted by equation 8.11 into the relative life expectation $\xi_{t,s,p,e,a}$ $\{\xi \in \mathbf{R} \mid 0 \leq \xi \leq 1\}$. The constant ρ_a indicates the relative life expectation, when the health condition of the retinal aspect at issue reaches its minimum (= 0). The simulation model makes use of the following constants: ρ_{ME}: 0.4; ρ_{PDR}: 0.4; ρ_{CA}: 0.3; ρ_{PV}: 0.3. Tests reveal that these values position the simulation close to epidemiologic findings [Davis 79; Knatterud 83].

The second step consists in determining the weighted average life expectation on the basis of the four retinal aspects of the left and the right eye. The condition of the macula and the peripheral retina are supposed to reflect the general health condition. This may be justified by reasoning in the opposite direction. A poorer general health condition is a simultaneous risk factor for the incidence of DR and death. Furthermore, death usually occurs, when the weakest indispensable body component fails. There-

fore in this calculation, weaker retinal aspects must have greater weight than stronger ones. Does a similar reasoning apply to vision? Sight enables surveying the environment to recognise or avoid dangerous situations. Vision deterioration impedes surveying the surroundings and increases the likelihood of accidents, both inside and outside the patient's home. Therefore, it makes death more probable. Vision depends primarily on the quality of the better eye. Consequently, the calculation of the hazard rate should give greater weight to the better eye. This is the opposite of the reasoning regarding the macula and the peripheral retina.

$$\overline{\xi_{t,s,p,mr}} = \frac{\sum_{e=\text{left}}^{\text{right}} \sum_{a=\text{macula}}^{\text{retina}} \frac{1}{(\xi_{t,s,p,e,a})^2} \xi_{t,s,p,e,a}}{\sum_{e=\text{left}}^{\text{right}} \sum_{a=\text{macula}}^{\text{retina}} \frac{1}{(\xi_{t,s,p,e,a})^2}} \tag{8.12}$$

Equation 8.12 formalises the analysis as to the macula and the peripheral retina. The weight factors consist of fractions, where the denominator represents the square of the relative life expectation for the retinal aspect at issue. Hence, the weight factors are inversely related to the relative life expectation. For reasons of clarity, equation 8.12 presents these factors completely. If $\xi_{t,s,p,e,a}$ equals zero, the equation becomes indeterminate. This cannot occur, however. Each ρ is greater than zero and x cannot reach zero, because x is determined by a logistic transformation (cf. equation 8.11). Equation 8.13 is a simplified version of 8.12.

$$\overline{\xi_{t,s,p,mr}} = \frac{\sum_{e=\text{left}}^{\text{right}} \sum_{a=\text{macula}}^{\text{retina}} \frac{1}{\xi_{t,s,p,e,a}}}{\sum_{e=\text{left}}^{\text{right}} \sum_{a=\text{macula}}^{\text{retina}} \frac{1}{(\xi_{t,s,p,e,a})^2}} \tag{8.13}$$

Equation 8.14 relates the relative life expectation to central acuity and peripheral vision. As the weight factors are the square of the relative life expectation, they increase exponentially when relative life expectation rises. Hence, the best vision has the greatest weight.

$$\overline{\xi_{t,s,p,cp}} = \frac{\sum_{e=left}^{right} \sum_{a=centralAcuity}^{peripheralVision} (\xi_{t,s,p,e,a})^3}{\sum_{e=left}^{right} \sum_{a=centralAcuity}^{peripheralVision} (\xi_{t,s,p,e,a})^2} \tag{8.14}$$

$$\overline{\xi_{t,s,p,mrcp}} = \frac{\sum_{b=mr}^{cp} \frac{1}{\overline{\xi_{t,s,p,b}}}}{\sum_{b=mr}^{cp} \left(\frac{1}{\overline{\xi_{t,s,p,b}}}\right)^2} \tag{8.15}$$

Equation 8.15 introduces some new symbols: mr: macula + peripheral retina; cp: central acuity + peripheral vision; mrcp: mr + cp. The equation presents the total average relative life expectation of a specific patient. Analogously to equation 8.12, the lowest average life expectation, determined by the equations 8.12 and 8.14, has the greatest weight.

$$\overline{\lambda_{s,p,mrcp(t)}} = \frac{\left(\overline{\xi_{t,s,p,mrcp}} - r\right) \lambda_{s,r+0.05(t+i)} + \left(r + 0.05 - \overline{\xi_{t,s,p,mrcp}}\right) \lambda_{s,r(t+i)}}{0.05} \tag{8.16}$$

$$\{r < \overline{\xi_{t,s,p,mrcp}} \leq r + 0.05 \mid r \in \{0.3, 0.35, ..., 0.95\}\}$$

After calculating the average relative life expectation $\overline{\xi_{t,s,p,mrcp}}$, the simulation determines the variable r according to the condition that accompanies equation 8.16. Consequently, r and r + 0.05 relate to the relative life expectation represented by the two most neighbouring vectors with hazard rates. In these vectors, the elements $\lambda_{s,r+0.05}(t+i)$ and $\lambda_{s,r}(t+i)$ are selected. Symbol i represents the age of incidence of DM. As the incidence coincides with t = 0, t + i represents the age of the patient. Then, the hazard rate $\overline{\lambda_{s,p,mrcp(t)}}$ of the patient is determined by linear interpolation.

$$\overline{\lambda'_{s,p,mrcp(t)}} = 1 - \sqrt[T]{1 - \overline{\lambda_{s,p,mrcp(t)}}} \qquad \{T \in \mathbf{Z}^+\} \tag{8.17}$$

This calculation faces two more complications. First, the model represents a patient's age by an unrounded real number. As a result, the age may not correspond to the number of a vector element. This problem is solved by linear interpolation. The second complication concerns determining the hazard rates per term ($\lambda'_{...}$) from yearly hazard rates ($\lambda_{...}$). These rates are evaluated by equation 8.17. The variable T indicates the number of yearly terms, that divide every year in T equal parts.

	Survival after 6 years of follow-up	Mortality density ratio
No retinopathy	95.9%	9.28
Mild diabetic retinopathy	91.4%	19.47
Moderately severe diabetic retinopathy	82.5%	39.61
PDR	66.2%	76.51
Visual acuity ≤ 20/40 (better eye)	89.9%	22.86
Visual acuity ≤ 20/200 (better eye)	57.9%	95.29

Table 8.2 - Six-year survival rates [Klein 84b, 89e] and mortality density ratios

Does this method, in combination with hazard rates published by the *Dutch Central Bureau of Statistics*, enable the simulation to tune mortality to evidence? To save space, the answer to this question is confined to IDDM patients. Klein and associates followed a cohort of 996 IDDM patients for six years. Initially, these patients were, on average, 29.3 years old. The second column of table 8.2 presents the observed survival rates classified with respect to the severity of DR and visual acuity. The third column states *mortality density ratios* reflecting how mortality among these patients relates to mortality in the general population of the Netherlands. The first ratio indicates for instance, that the hazard rates of diabetic patients without DR equal 9.28 times the hazard rates of the general population[8]. These *mortality density ratios* are founded on the statistics in table 8.3 and in the second column of table 8.2.

Age	Survivors in cohort of 100,000 live births (either F or M)	
	Females	Males
29.5	98,520	97,678
35.5	98,117	97,155

Table 8.3 - Survivors in the general population of the Netherlands [CBS 88b:44-5]

Starting from table 8.3, equation 8.18 determines the likelihood, that a person in the general population of the Netherlands passes away within six years after reaching the age of 29.5 years. The calculation is based upon an unweighted average, because the

8 These calculations start from the presumption, that the mortality rates for the relevant age group of the general population in the Netherlands do not differ significantly from the corresponding rates in the United States.

birth surplus of boys is virtually neutralised at that age by higher hazard rates for men. The symbols D and L indicate respectively *deceased* and *alive*, while the subscripts refer to ages.

$$P(D_{< 35.5} \mid L_{29.5}) = \frac{\left(1 - \frac{98,177}{98,520}\right) + \left(1 - \frac{97,155}{97,678}\right)}{2} \approx 0.004417927 \qquad (8.18)$$

Substituting the result of 8.18 in 8.19 discloses, that the mortality risk over a period of six years is 9.28 times higher for 29.5-year old IDDM patients without retinopathy, indicated by the symbols IDDM ∩ noDR, than for members of the general population [calculation after: Kleinbaum 82:149].

$$\frac{P(D_{< 35.5}^{\text{IDDM} \cap \text{noDR}} \mid L_{29.5}^{\text{IDDM} \cap \text{noDR}})}{P(D_{< 35.5} \mid L_{29.5})} = \frac{\frac{100 - 95.9}{100}}{0.004417927} \approx 9.28 \qquad (8.19)$$

The *Mortality density ratios* for other patient groups in table 8.2 are determined analogously[9]. Apparently, the prevalence of DM raises hazard rates considerably. Moreover, there are sizeable differences between IDDM patients. Consequently, the severity of DR, and even more so blindness, clearly raises hazard rates. Broadly speaking, the results of the DRS correspond with the findings of Klein and co-workers [Knatterud 83].

An investigation of 1,470 diabetic patients by Palumbo et al. [76] reveals also, that DM restricts the relative life expectation. Twenty years after the diagnosis of DM (IDDM or NIDDM), the relative number of survivors was 31% smaller than in the general population. From 1961 to 1977, Davis and associates [79] studied 588 patients in a diabetic retinopathy clinic plus 190 primary care patients in the American state Wisconsin. For 709 patients, DM was diagnosed before the age of 50 years (mean: 22.2 years). Hence, the study population comprises many IDDM patients. The investigation presents five-year survival rates classified according to the severity of DR, like the following: ME 0.81; PDR 0.56; {20/200 < visual acuity < 20/40} 0.65 and 0.59 (PDR);

9 Table 8.2 presents these ratios with an accuracy of two decimals. It aims at providing full information, so that the numbers can be checked. The actual accuracy is however limited for the following reasons: (1) at the start of the study by Klein and associates, the average age of the population was 29.3 years (standard deviation 13.3 years); (2) Dutch hazard rates differ from American rates; (3) life tables by the CBS present statistics for the age of 29.5 years, not for 29.3 years. Consequently, the mortality density ratios mentioned in table 8.2 do not pretend to quantify mortality differences exactly. They merely want to depict the order of magnitude of differences (1) between diabetic patients and the general population and (2) among diabetic patients themselves.

legally blind (≤ 20/200) 0.20 and 0.43 (PDR). Dorman et al. [84] studied 1,966 IDDM patients from 1950 to 1981. After the age of twenty, the hazard rates in this population equalled twenty times the rates of the general population in the United States.

These three investigations confirm, that the progression of DR as well as changes in visual acuity significantly affect the hazard rates of diabetic patients. The simulation implements this relationship by the equations 8.11 to 8.16 and by the parameters about the relative life expectation - ρ_{ME}, ρ_{PDR}, ρ_{CA}, ρ_{PV} - that were introduced with reference to equation 8.11. The parts C and D of this manuscript mention the life expectation determined by this method for various groups of diabetic patients.

8.8 Screening & Treatment

Figure 8.11 (page 116) presents the module *Screening & Treatment*. The structure of the diagram differs from previous diagrams for two reasons. First, this module mainly accommodates decision making statements. They create a network of paths into which an arrow diagram gives more insight. Second, decision making statements require less space in an arrow diagram. Consequently, one page suffices to present the entire module schematically[10].

In the simulation, all patients comply strictly with ophthalmic screening guidelines. This is inconsistent with the findings presented in section 3.5. Both in the Netherlands and in the United States, a considerable number of diabetic patients disregard these guidelines [Verhoeven 89:70; Dasbach 91]. There are few reasons to assume, that the situation is more auspicious in other countries. Nonetheless, the presumption of perfect compliance does not impair the validity of the model. Every simulation contains five scenarios with different intensities of ophthalmic care, indicated by table 8.1 in section 8.4. As all patients follow the screening guidelines strictly, it is easy to determine how the results of several scenarios should be mixed to compose a *"cocktail"* that corresponds with the observed compliance. Obviously, the weight of each scenario in this cocktail depends on the relative number of patients that actually follow that specific

10 Figure 8.11 reflects the understanding and expertise by prof.dr. F. Hendrikse (Professor of Ophthalmology, Department of Ophthalmology, University of Limburg Medical School, Maastricht) and prof.dr. P.T.V.M. de Jong (Professor of Ophthalmology, Department of Ophthalmology, Erasmus University Medical School, Rotterdam). Their support was essential, because this scheme constitutes the cornerstone of the simulation model. Herewith, I do acknowledge my gratitude for this crucial help.

scenario. Consequently, this assumption gives the simulation model a wider applicability than models that investigate one particular compliance mix. In other words, this presumption is an enrichment rather than an impoverishment.

The module *Screening & Treatment* models the practice of ophthalmic examinations and laser treatments. However elaborate the model may be, it can never fully do justice to the complexity of reality. Hence, this module aims merely at describing and analysing the most typical situations. First, the patient's visual acuity is determined by a perfectly sensitive and specific test. Then, ophthalmoscopy follows. The quality of this examination depends on the actual state of the retina. As the condition of the retina approaches a border value, the diagnosis becomes less reliable. Implementing this refinement requires a simulation that represents the condition of the retina by a continuous scale, as section 4.3 emphasises. Figure 8.10 indicates, how the condition of the retina affects the sensitivity and the specificity of ophthalmoscopy. The variables se_{BR} and sp_{BR}, respectively the sensitivity and the specificity when diagnosing *BR*, reach their lowest value on the border line of *noDR* and *BR*. At the border of *BR* face to *PDR* and *ME*, the same is *ipso facto* valid for se_{ME}, se_{PDR}, sp_{ME}, and sp_{PDR}.

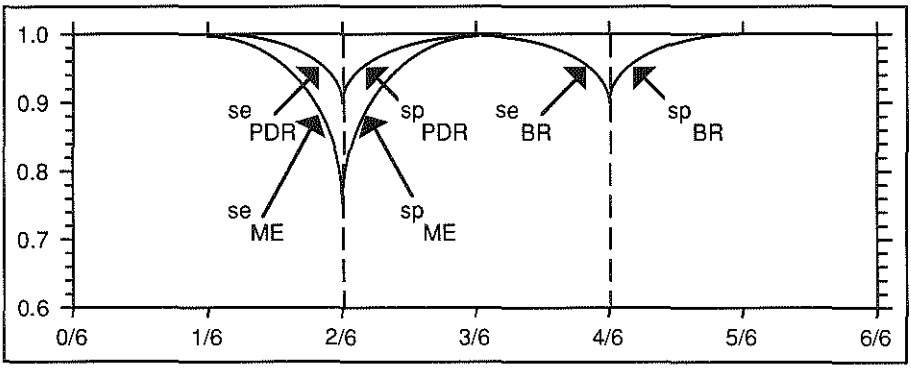

Figure 8.10 - Sensitivity and specificity (y-axis) as function of retinal condition (x-axis)

The curves in figure 8.10 rest on the equations 8.20 and 8.21, which constitute a theoretical model. $P(T^+ \mid D^+)$ indicates the sensitivity, being the likelihood of a positive test (T^+) if the disorder is present (D^+). *Mutatis mutandis*, $P(T^- \mid D^-)$ refers to specificity. P_{min} represents the minimum value of the sensitivity (in 8.20) or the specificity (in 8.21), while x_b is the border value of D^+ and D^-. In equation 8.20, x_c is the highest value of $x_{t,s,p,e,a}$ $\{0 < x_{t,s,p,e,a} < 1\}$, where the sensitivity equals 1 $\{x_c < x_b\}$. In equation 8.21, x_c is the lowest value of $x_{t,s,p,e,a}$, where the specificity equals 1 $\{x_c > x_b\}$. Furthermore, equation 8.20 reveals, that $P(T^+ \mid D^+)$ is not defined for

$x_{t,s,p,e,a} > x_b$, because the disorder is absent. Similarly, $P(T^- | D^-)$ is not defined for $x_{t,s,p,e,a} < x_b$.

$$P(T^+|D^+) = \begin{cases} P_{min} + (1 - P_{min}) \sqrt[4]{\dfrac{x_b - x_{t,s,p,e,a}}{x_b - x_c}} & \{x_c \le x_{t,s,p,e,a} \le x_b\} \\ 1 & \{x_{t,s,p,e,a} < x_c\} \end{cases} \quad (8.20)$$

$$P(T^-|D^-) = \begin{cases} P_{min} + (1 - P_{min}) \sqrt[4]{\dfrac{x_{t,s,p,e,a} - x_b}{x_c - x_b}} & \{x_b \le x_{t,s,p,e,a} \le x_c\} \\ 1 & \{x_{t,s,p,e,a} > x_c\} \end{cases} \quad (8.21)$$

The progression of the sensitivity and the specificity, generated by these equations, follows the main lines of well-known probability density distributions concerning continuous observation results [Giard 89:92-3]. However, the available evidence does not provide sufficient support to determine the structure and the parameters of these equations. Hence, they mainly depend on assumptions. Table 8.4 presents the minimum values of the sensitivity and the specificity that appear in figure 8.10.

	Sensitivity	Specificity
BR	90%	90%
ME	75%	75%
PDR	90%	90%

Table 8.4 - Minimum values of sensitivity and specificity

Medical publications offer quite diverging data on the sensitivity and specificity of ophthalmic examinations. Section 3.5 presented some findings [Williams 86; Javitt 90; Buxton 91; Dasbach 91]. Recently, Sculpher et al. [92] published the following results: sensitivity 40% to 80% and specificity 86% to 97% in screening for DR. These percentages relate to six diagnostic options: ophthalmoscopy by (1) general practitioners and (2) ophthalmic opticians; non-mydriatic 45° photography in (3) hospitals and (4) general practices; (5, 6) two combinations of the methods (1...4).

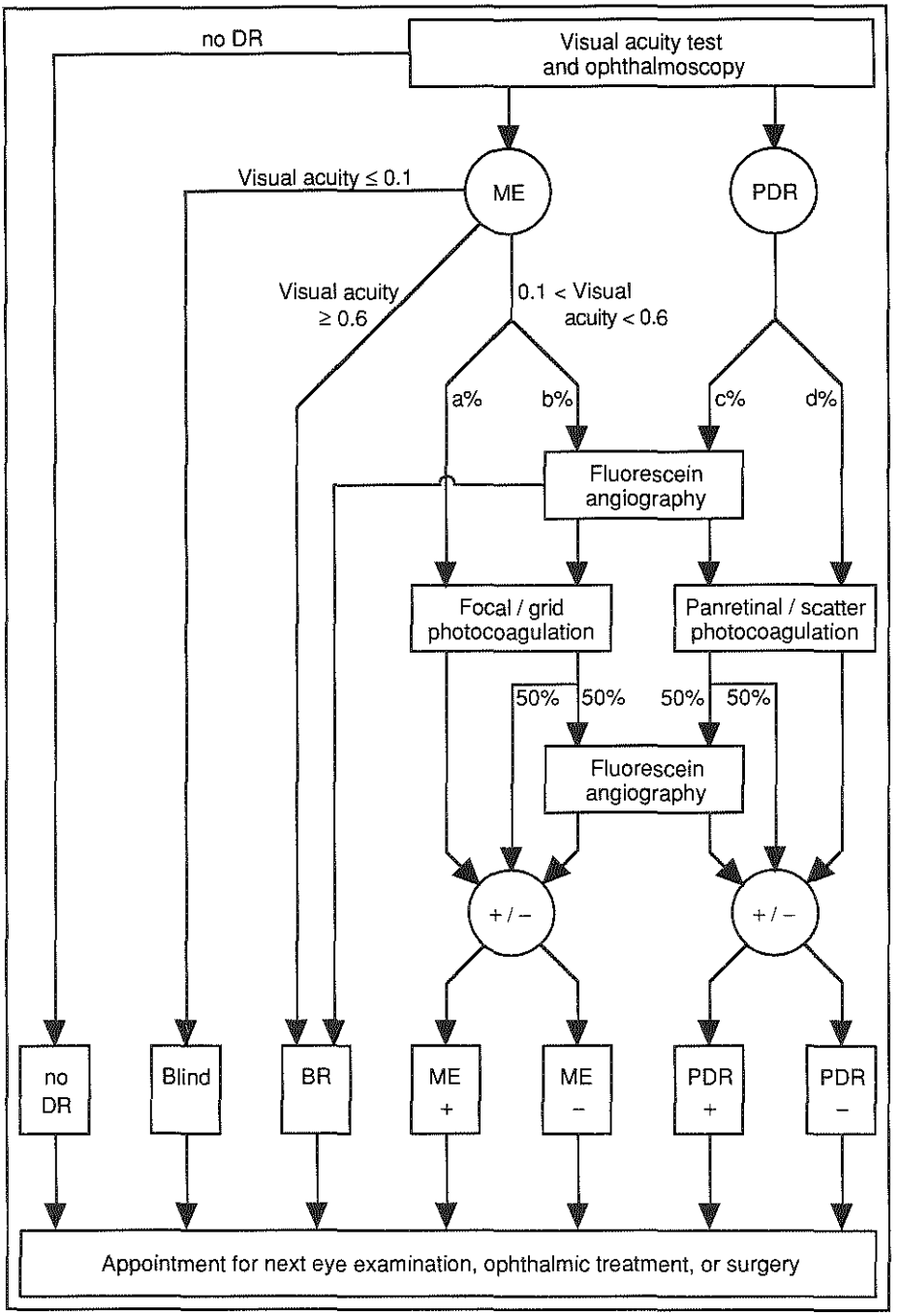

Figure 8.11 - The module *Screening & Treatment* (a%, b%, c%, d%: cf. table 8.5, p. 118)

The disparity of data impedes a choice that satisfies everyone, above all because the findings originate from quite divergent situations. Therefore, the values in table 8.4 constitute a compromise. They reflect (1) the advice of distinguished ophthalmologists, (2) the results of the previously mentioned investigations, and (3) the actual situation in Dutch ophthalmic clinics. The simulation is confined to eye examinations by ophthalmologists. This choice relates to the present ophthalmic practice in the Netherlands and in neighbouring European countries - Belgium, France, Germany - where the number of ophthalmologists is comparatively larger than in the Netherlands. Although the cost-effectiveness of mydriatic fundus photography is a subject of investigation in the Netherlands (cf. footnote 2, chapter 3), ophthalmoscopy by ophthalmologists will probably remain the most important screening technique in the near future.

Let us now return to figure 8.11. If ophthalmoscopy does not discover retinal disorders, the diagnosis is *noDR* and a new examination date is determined according to the guidelines of the scenario at issue. Otherwise, DR is diagnosed. If visual acuity equals 0.1 (20/200) or less, the eye is blind and receives no treatment. A new screening appointment is made, mainly for humanitarian reasons. If the retinal disorders are mild and visual acuity equals 0.6 (≈ 20/33) or more, the diagnosis is *BR*. Then, laser treatment is not indicated and a new screening date is set. The scheme respects the guidelines agreed to at the consensus meeting (November 1, 1991) organised by the *Dutch Scientific Council of Medical Quality Assurance* in co-operation with the *Netherlands Academy of Ophthalmology* [Hendrikse 92]. The only difference concerns the latter limit. In figure 8.11, it equals 0.6, while there was agreement on 0.5.

After the diagnosis *ME* or *PDR*, the ophthalmologist examines some patients by fluorescein angiography (FA). According to the presumptions of the model, this test relates to both eyes[11]. It has a twofold aim. First, it may correct diagnostic errors, so that false positive eyes are diagnosed as true positive. In figure 8.11, the arrow from the upper block *Fluorescein angiography* to the diagnosis *BR*[12] indicates this correction. Second, FA is superior in assessing the leakage of retinal vessels in the macular area (cf. section 3.5). Therefore, FA forms a complement to ophthalmoscopy.

11 Although the left and the right eye traverse the module Screening & Treatment separately, the maximum number of fluorescein angiograms before laser treatment equals one per patient per treatment session. After laser treatment, the same maximum applies.

12 The simulation model presupposes, that the difference between the diagnosis and the actual condition never exceeds one category in the classification of DR. This hypothesis excludes, for instance, the diagnosis *ME* or *PDR* for patients without DR.

	ME		PDR	
	no FA	FA	FA	no FA
	a%	b%	c%	d%
Option α	25%	75%	25%	75%
Option β	50%	50%	10%	90%

Table 8.5 - Two diagnostic options (cf. figure 8.11)

During this consensus meeting, no agreement was reached on the indication of FA [Hendrikse 92]. Therefore, the simulation model uses the options α and β. Table 8.5 mentions, how frequently FA is applied in both options following the diagnosis *ME* and *PDR* respectively. The symbols a%, b%, c%, and d% in figure 8.11 are substituted by these frequencies. In part C and part D, the results of the options α and β are presented separately, if they differ significantly.

When *ME* is discovered, the eye receives a focal or grid laser treatment, whereas *PDR* is followed by panretinal or scatter laser treatment, as indicated in section 3.6. Focal treatments comprise a series of two sessions, grid treatments one session and panretinal or scatter treatments four sessions. For the sake of simplicity, the model assumes, that a series is completed by the end of the term in which it starts. Half the patients who underwent FA before the treatment, have FA thereafter as well.

According to the two large-scale investigations mentioned previously [DRSRG 81; ETDRSRG 85, 91b], photocoagulation reduces the risk of severe vision loss by 50% in treating *ME* and by nearly 60% regarding *PDR*. As indicated in section 3.6, successful treatments of *ME* imply that the macula and central acuity deteriorate at half their *"natural"* speed. Success in treating *PDR* leads to the stabilisation of the peripheral retina and peripheral vision. After unsuccessful treatments, the disease progression of the macula or the peripheral retina maintains the same course as in the absence of treatment.

Figure 8.11 presents two circles holding the symbols +/–. They symbolise the generating of random numbers to determine, whether treatments are successful or not. For that purpose, these numbers are compared with success rates. It may seem obvious to borrow these rates directly from the investigations mentioned in the previous paragraph. Section 4.3 emphasises however, that the effectiveness of laser treatments depends on the condition of the retina. For the simulation, this relationship is crucial, because intensifying ophthalmic care reduces the chance that patients are screened, when the progression of DR precludes effective laser treatment. A simulation that ignores this essential relationship seems poorly suited to investigating, whether intensifying

eye care may prevent blindness. If the model would use average success rates, the effectiveness of treatments is not related to the retinal condition. This seriously obstructs approaching the key problem of this investigation adequately. Although empirical findings lack, this simulation may not neglect this fundamental relationship. From sheer necessity, it uses presumptions. However, as soon as empirical results appear, they can be incorporated in this model immediately.

$$P(P^+) = \frac{P_{max}}{1 + e^{-a\,(x_{t,s,p,e,a} - h)}} \qquad \{a,h,P_{max} \in \mathbf{R} \mid a > 0;\ 0 < h;\ 0 \le P_{max} \le 1\} \quad (8.22)$$

Equation 8.22 formalises the success rate of laser treatments $P(P^+)$ as an S-curve. P_{max} is the maximum value of $P(P^+)$, a is a coefficient and h symbolises the value of x, where $P(P^+)$ equals 0.5 P_{max}.

	ME	PDR
P_{max}	0.67	0.73
a	256.00	256.00
h	0.32	0.32

Table 8.6 - Parameters in equation 8.22

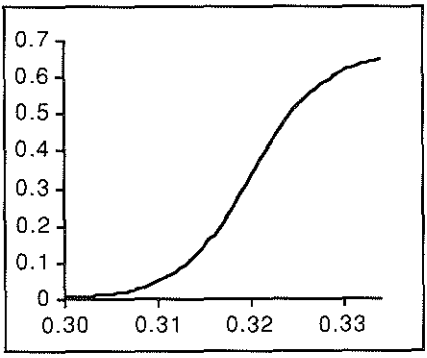

Figure 8.12 - Success rates focal/grid laser treatment (ME)

x	ME	PDR
0.300	0.0040	0.0044
0.303	0.0085	0.0093
0.306	0.0180	0.0198
0.309	0.0376	0.0414
0.312	0.0762	0.0838
0.315	0.1450	0.1595
0.318	0.2498	0.2748
0.321	0.3758	0.4133
0.324	0.4905	0.5396
0.327	0.5714	0.6286
0.330	0.6188	0.6807
0.333	0.6436	0.7079

Table 8.7 - Success rates laser treatment

Table 8.6 indicates the values of these parameters in the simulation. Table 8.7 describes the progression of the success rates in the treatment of *ME* and *PDR* as a function of the retinal condition x. Figure 8.12 presents the statistics of table 8.7 graphically for *ME*. If the success rate is less than 5%, the eye receives no laser treatment, following model assumptions.

After successful laser treatment, the eye is classified in category ME^+ or PDR^+, otherwise in category ME^- or PDR^-. Finally, a date is fixed for the next ophthalmic examination, treatment, or surgery, like trans pars plana vitrectomy. Given the demarcation of this investigation, the model ignores surgery and treatments other than photocoagulation. As appears from ophthalmic practice, some eyes with exudative DR and visual acuity ≥ 0.6 receive focal laser treatment. Figure 8.11 does not represent such cases, as they are rather exceptional.

The stepwise review of figure 8.11 discloses, why the left and the right eye traverse this scheme separately. There are four exceptions, however. (1) The diagnosis *blindness* depends on visual acuity of the better eye, following the definition in section 7.3. (2)(3) The technique of FA involves injecting a solution of sodium fluorescein into the antecubital vein. Then, both eyes may be photographed [L'Esperance 90:675]. (4) The model determines the next screening date twice, but it memorises the earlier date only. Both eyes are to be examined at that date.

The differences between the options α and β not only concern the frequency of FA, but also to the duration of treatment effectiveness. Option α assumes that successful treatments are effective until death. If photocoagulation is not successful, no second treatment follows for the same disorder. In other words, a treatment is a one-off and definite event. The maximum number of laser treatments per patient equals four, as the simulation distinguishes both eyes plus the macula and the peripheral retina. The success rate depends only on the state of the retinal aspect at issue. Hence, this rate may differ considerably for different treatments given to the same patient. Despite this disparity, there may be cohesion concerning the effectiveness of different treatments for one patient. It results from the coherence of value assignments to different retinal aspects, illustrated by figure 7.6 in section 7.6. Hence, various retinal aspects progress rather symmetrically. As this development is an important determinant of the success rate, the success rates of different treatments for one particular patient may also reveal some symmetry.

In the simulations by Javitt et al. [89, 90, 91], laser treatments have permanent effects. Moreover, there is some correlation of treatment outcome between both eyes. The simulation by Dasbach and associates [91] distinguishes neither left and right eyes nor the macula and the peripheral retina. It offers each patient not more than one laser treatment until its end point.

According to the assumptions of option β, successful treatments are temporarily effective. They are repeated several years later. For this option, the simulation puts the dis-

ease progression of a retinal aspect five years back after successful treatment[13]. The progression of that retinal aspect then pursues its "natural" course determined by the method described in chapter seven. Consequently, five years elapse on average before another treatment follows. Many patients, in particular NIDDM-patients, do not survive more than five years after the first laser treatment. Hence, the total number of laser treatments differs modestly in both options.

8.9 Simulation Conclusion

After processing all scenarios, the simulation activates the module *Simulation Conclusion* to release random access memory for other processes and to close output files. These are then accessible for further analysis in other software. Part C and part D present results of this operation.

13 Conceptually, the simulation model is capable of recording the retinal condition for all the previous periods of the analysis. These statistics require a vast amount of internal computer memory. For technical reasons, the cohort size must therefore be reduced considerably, even if a desktop computer is available with a rather large internal memory for present standards (8 megabytes). The reliability of a Monte Carlo analysis increases significantly, if the cohort size grows, at least up to some 10,000 patients [Beck 83]. Consequently, the price for storing results of previous periods is too high. The simulation model uses an approximation method that requires no supplementary storage space. The z-value $z^c_{t,s,p,e,a}$ is determined by the parameters $\mu_{t,a}$ and $\sigma_{t,a}$ of a normal distribution representing the prevalence in period t in the interval $(-\infty, +\infty)$ and by $y^c_{t,s,p,e,a}$. Then, $y^c_{t,s,p,e,a}$ is set at: $\mu_{t-5,a} + \sigma_{t-5,a} z^c_{t,s,p,e,a}$ $\{t \in \mathbf{R} \mid t \geq 5;$ t expressed in years$\}$.

9

Costs, Effects, and Benefits

9.1 Introduction

As the simulation follows every patient individually, vast quantities of data emerge. They measure the retinal condition and visual acuity as well as the quantity of ophthalmic care that every person receives. The model summarises these findings annually by calculating totals. Most of them express the absolute prevalence of different grades of DR and visual impairment, as well as the number of ophthalmic tests and treatments. After determining these totals for five scenarios, the results are compared with one another. Then, the following distinction emerges: the number of ophthalmic examinations and treatments relate to *costs* of ophthalmic care, while the prevalence of visual impairment reflect *effects*.

Both concepts demand marginal notes. Besides statistics on screening and treatment quantities, information on prices is required for calculating costs. Subsequent sections in this chapter will present details on this issue together with a justification. The notion *effects* may suggest that the simulation measures the comfort of ophthalmic care in physical units only. This is true for the most important effect, vision maintenance, because rather few attempts have been made so far to express the consequences of vision loss in utility, for instance by means of QALYs - *Quality-Adjusted Life-Years* [Drummond 86, 88, 90; Ferguson 88, 90:88-9]. These investigations do not provide sufficient support for consensus. Moreover, QALYs call forth methodological objections [Avorn 84; Blades 87; Behrens 88; Hodgson 89]. Finally, medical publications provide insufficient support for determining the monetary value of vision preservation.

Some consequences of vision conservation, however, can be expressed in money. According to the classification by Drummond and co-workers, they comprise direct and indirect benefits [87:23]. In this investigation, direct benefits consist of savings in disability facilities, whereas indirect benefits refer to production growth enabled by re-

ducing visual impairment. This chapter presents these issues while admitting that they are also subject to debate.

The next sections examine *costs* as well as *effects* and *benefits* following four steps: (1) demarcating, (2) detailing, (3) volume determining and, if necessary, (4) value establishing. Prior to this, some issues are discussed that are simultaneously relevant to costs, effects, and benefits: (1) discounting, (2) average and marginal analysis, (3) market prices versus *willingness to pay*, and (4) *human capital approach* versus *friction costs*.

9.2 Discounting

Costs generally precede effects and benefits. This sequence also characterises ophthalmic care for diabetic patients. Only after eye examinations and laser treatments, vision loss may be prevented. Consequently, costs, effects, and benefits occur at dissimilar moments. This provokes measurement problems related to time preference. There are two sides to this phenomenon. Most people want to enjoy benefits or pleasant events as soon as possible, whereas they like postponing costs or displeasing experiences *ad infinitum*. Consequently, benefits and costs increase their weight by occurring earlier. *Ipso facto*, deferral reduces their weight.

$$\left|E_r^p\right| > \left|E_{r+\rho}^p\right| \quad \{p, r, \rho \in \mathbf{R} \mid \rho > 0\} \tag{9.1}$$

Inequality 9.1 formalises this relationship. The symbols $E^p{}_r$ represent the value at time p of event E occurring at time r. Because ρ is greater than zero, the right side of the inequality is smaller than the left side, although both sides relate to the same event. If E can be expressed as a real number, E may be positive or negative. The analysis skips zero, because this number represents events to which people are indifferent. The difference between the left and the right side of equation 9.1 indicates the absolute time preference, whereas the quotient indicates the relative time preference without connection to the value of E.

$$E_r^p = (1+i)^{p-r} E_r \quad \{E, i, p, r \in \mathbf{R}\} \tag{9.2}$$

Discounting is common practice in economic assessments of health care projects. It enables the analyst to determine the weight of costs, effects, and benefits at one specific moment, although they may be spread in time. Essentially, this technique is founded

on the following multiplication factor[1]: $(1 + i)^t$. Symbol i indicates the discount rate reflecting the time preference, whereas t is the time difference between moment r when the event actually occurs and moment p when its value is calculated by equation 9.2 ($t = p - r$).

If i is greater than zero and r precedes p, the multiplication factor exceeds 1 and the discounted value surpasses the actual value. When r follows p, the factor has a value between zero and one ($i > 0$). In that case, the discounted value falls short of the actual value. Costs, effects, and benefits may cover different periods. Then, they should be specified per period and the multiplication factor is applied to each period separately with the appropriate value of t. Any unit of time is acceptable, provided i and t are expressed in the same unit. Finally, discounting is based on the assumption that the time preference is constant during the time interval between p and r.

Discounting allows the inclusion of the factor time preference in project comparisons. As a rule, this factor is positive, so that it results in a positive discount rate. Consequently, the weight of an event increases, as it occurs earlier. Discount rates provide criteria for ordering projects and for making strategic choices, when staff, equipment, or finances create limiting conditions. Discount rate fluctuations may alter the balance of costs and benefits dramatically, as well as the order of projects. At higher discount rates for instance, emergency care may appear relatively more advantageous than preventive care, because the effects of the former precede the blessings of the latter. Therefore, the choice of the discount rate may have far-reaching consequences.

Discount rates should only reflect time preference. This statement precludes equating discount rates to interest rates in financial markets, because the latter reflect the interaction of demand and supply. They therefore depend simultaneously on the marginal time preference and the marginal rate of return on investment. Questionnaires might offer a superior alternative by focusing exclusively on time preference. However, this technique evokes serious objections that the following questions implicitly reflect. Do the answers correspond with actual behaviour? What weight should each question have? What is the relative importance of the answers by different persons? Is the sample unbiased? And is the response sufficient? Apart from this, questionnaires are quite time-consuming and costly.

1 This multiplication factor applies, if the time is regarded discretely. In case the time is considered as a continuous variable, the multiplication factor equals $e^{i\,t}$ $\{i, t \in \mathbf{R}\}$. Footnote 2 in chapter 4 is based on a discrete approach.

Because of these problems, discount rates are usually derived from interest rates on money (short-term) and bond (long-term) markets. These rates indicate the actual behaviour of a large number of persons and organisations, as well as their relative weight. Most information on interest rates is reliable, inexpensive, and up to date. At the demand side of financial markets, the interest rate is the price for advancing purchasing power. At the supply side, it is the reward for waiting. Thus, financial markets reflect the desire to command goods and services earlier. Time preference is a major determinant of interest rates, according to this view.

In this context however, interest rates have important disadvantages. As mentioned above, they simultaneously reflect two rates: (1) the marginal time preference and (2) the marginal rate of return on short-term or long-term investment. Interest rates equal both rates simultaneously, provided market imperfections are absent. Hence, markets should satisfy the following conditions: (1) numerous sellers and purchasers, (2) homogeneity of product, (3) freedom of entry and exit, (4) perfect information, (5) no risk or uncertainty, and (6) no taxes or subventions [SDMF 85 (Minderheidsstandpunt):3; Baumol 88:558]. As these conditions are never satisfied simultaneously, it seems unavoidable to select one of these two rates. Empirical findings do not support this choice adequately, however [Klaassen 90:204]. Frequently, the long-term rate of return on investment is considered as an acceptable alternative, because it reflects observable and operational behaviour [SDMF 85:1].

To preclude inflation[2] effects, discounting may be based on real interest rates, that are derived from nominal interest rates by corrections for changes of the price index[3] [SDMF 85:2]. Apart from complications in determining the inflation rate, real interest rates create new problems by their fluctuations. The annual rate equalled 3% to 4% between 1900 and 1940. It fell to nearly 1% from 1950 until the start of the eighties and approximated 5% in recent years [SDMF 85:39-40]. How do these fluctuations, or expected fluctuations, affect the selection of long-term projects? No consulted publication answers this question [cf. (besides previous references) COBA 74; Mooney 80; Thompson 80; Mishan 82; Warner 82; Cohen 88; McGuire 88; Krahn 92].

2 In this publication, the concept *"inflation"* is confined to rises in the general price level, corresponding to decreases in the purchasing power of money. Elsewhere, *"inflation"* may indicate increases in the money supply.

3 Strictly speaking, the real interest rate equals $(1 + i) / (1 + p)$. The symbol i represents the nominal interest rate, whereas p indicates the relative change of the price index. At smaller values of i and p, this quotient equals $i - p$ approximately.

At the beginning of the seventies, the official discount rate equalled 10% in France, the Netherlands, the United Kingdom, and the United States [COBA 74:20-1]. In subsequent years, the Treasury of the United Kingdom advised discounting at 5%, 6%, and 7%, but recommended a lower rate for utility measures [Mooney 80:56; Cohen 88:91]. At present, the Government of the United Kingdom no longer maintains an official discount rate [Krahn 92:2]. The Government of the Netherlands modified the official real discount rate in 1986 from 10% to 5% [ABMF 86:175]. Despite fluctuations of long-term interest rates, the discount rate remained unaltered subsequently. Therefore, the next paragraphs present a brief investigation.

Some authors opt for an annual discount rate of 5% [Guyatt 86; Eisenberg 89; Dasbach 91; Javitt 91]. Avorn [84] objects, however, that this choice lacks empirical backing. For that reason, the simulation looks for guidance on loan markets. There, interest rates comprise four components: (1) the pure interest rate representing time preference, (2) the compensation for inflation, (3) administration charges, and (4) the premium to cover insolvency risks. At any one moment, loan markets present a wide spectrum of interest rates, mainly because the third and the fourth component may vary considerably from loan to loan. In this spectrum, the interest rates on the money and the bond market are standards for short-term and long-term loans respectively. In these markets, interbank loans have a substantial share. Their size renders administration charges relatively insignificant, while the risk of insolvency is rather small. Consequently, the money and bond market interest rates reflect approximately the pure interest rate plus the compensation for inflation.

(percentages)	Short-term interest rate (average rate December)			Long-term interest rate (average rate December)			Price index national product (annual increase)			Short-term interest rate minus increase price index			Long-term interest rate minus increase price index		
	1988	1989	1990	1988	1989	1990	1988	1989	1990	1988	1989	1990	1988	1989	1990
Belgium	7.4	10.1	9.9	8.1	9.6	10.0	3.1	4.4	4.2	4.3	5.7	5.7	5.0	5.2	5.8
Denmark	8.0	12.0	10.4	10.4	10.5	11.0	4.1	4.7	3.7	3.9	7.3	6.7	6.3	5.8	7.3
France	8.5	10.8	10.3	8.6	9.1	9.9	3.1	3.2	3.2	5.4	7.6	7.1	5.5	5.9	6.7
Germany	5.3	8.1	9.1	6.5	7.4	8.8	1.9	2.7	4.2	3.4	5.4	4.9	4.6	4.7	4.6
Italy	11.9	12.8	12.7	10.7	12.3	12.0	6.7	6.6	6.8	5.2	6.2	5.9	4.0	5.7	5.2
Japan	4.2	5.8	7.6	4.1	5.7	7.1	0.7	2.7	1.7	3.5	3.1	5.9	3.4	3.0	5.4
Netherlands	5.7	8.6	9.4	6.4	7.8	9.1	0.7	2.3	2.7	5.0	6.3	6.7	5.7	5.5	6.4
United Kingdom	12.6	14.5	13.2	9.5	10.0	10.4	8.1	5.8	6.8	4.5	8.7	6.4	1.4	4.2	3.6
United States	9.3	8.3	7.8	9.0	7.9	8.2	4.1	3.7	4.0	5.2	4.6	3.8	4.9	4.2	4.2
Average										4.5	6.1	5.9	4.5	4.9	5.5
Average 1988-1990											5.5			5.0	

Table 9.1 - Short- and long-term real interest rates in 9 countries [DNB 91:36-7 (stat suppl)]

For nine countries, the columns 2 to 7 in table 9.1 indicate short-term and long-term nominal interest rates in 1988, 1989, and 1990. The columns 8 to 10 specify yearly increases in the price index of the national product. Arbitrarily, this price index is selected as the standard for measuring inflation. The last six columns present real interest rates, that correspond to the difference between nominal interest rates and increases in the price index. These real interest rates may be considered as acceptable approximations of the pure interest rate, or the social time preference. The last line indicates two unweighted means. The unweighted average of all short-term and long-term real interest rates equals 5.2%. This level is substantially higher than in the fifties, sixties, and seventies. Then, real interest rates fluctuated around 0% in the United States [Lipsey 84:685].

This brief investigation may justify fixing the discount rate at 5%, especially because Drummond and associates argue, that this percentage facilitates comparing different projects [87:49]. However, this recommendation may invite a marginal note. Elementary numerical examples illustrate, that changes in the discount rate may alter the order of projects significantly. This is contrary to the requirement of consistency. If person A is taller than person B when measured in meters, A should be taller than B when measured in any other unit. As opposed to selections of length units, choices of discount rates implicate subjective judgements.

The relationship between social and individual time preferences may be an even more fundamental problem than the previous one [Cairns 91]. It does not seem unreasonable to suggest, that human society has a broader time horizon than individual persons, whose life expectation is limited. However, many parents and grandparents have strong commitments to future generations through their children and grandchildren. This controversy has a long history of debate. During the Graeco-Roman Eras and the Middle Ages, philosophers and theologians dedicated numerous dissertations to the *justum pretium*, emphasising the question of the proper price for loans. Respecting their ethical and religious principles, they state that money lenders should avoid usury out of love for neighbours. Since the renaissance, profits and interest revenues receive greater sympathy following the advent of a more individual concept of man [Zimmerman 57:14-20; Gide 60:514, 534; Nentjes 83:3].

Although this debate may appear out of date because of its long history, it is of current interest, not the least in health care. Present political decisions have short-term as well as long-term consequences. It is quite conceivable for instance, that our polluting the environment and exhausting irreplaceable stocks of fossil energy and raw materials jeopardise the welfare of future generations. Therefore, discounting is a momentous

subject of a debate that accentuates the distinction between individual and social interests [Lancet 92]. Should social interests have a higher priority than individual claims in order to secure future happiness and prosperity at the expense of present well-being? [Rouwendal 85]

In the context of this debate, Iwema and Klaassen [81] present the *generation preference rate* to refine the technique of discounting. Their model presumes, that generations do not overlap. It uses more than one reference moment for discounting. The discounted value of costs and benefits realised during the active life of a specific generation is determined at beginning of the first year, when that generation appears. If each generation is active for 25 years, the discounted value of costs and benefits gained during the years 1 to 25 is determined at the beginning of year 1. The start of year 26 is the reference moment for discounting costs and benefits realised during the years 26 to 50, and so on. Apart from adjustments, this implies that benefits of $ 100 gained at the start of year 10 have the same discounted value as benefits of $ 100 realised at the beginning of year 60. These discounted values are adjusted by the *generation preference rate* γ. Generally, γ borrows a real number from the interval [0, 1]. If γ equals 0.9 for instance, costs and benefits are discounted by the technique described earlier in this paragraph. Then, the discounted values related to generation two, three, four ..., n are multiplied by 0.9, 0.81, 0.729, ..., 0.9^{n-1} respectively. As compared to the *"classical"* discounting method, this technique enables emphasising the interests of future generations. It has important shortcomings, however.

First, it seems quite unfeasible to determine the *generation preference rate* empirically. Second, this technique creates curious discontinuities in the progression of discounted values. Following the previous example, the discounted value of $ 100 realised at the end of year 25 equals $ 29.53 at an annual discount rate of 5%. If the same amount is situated one moment later, at the start of year 26, its discounted value is $ 90. According to Klaassen and Weehuizen [82], the *"classical"* discounting technique, after reducing the discount rate, may generate the same discounted value for a project as the *generation preference rate* technique. In this view, the latter technique implicates a disguised decrease in the discount rate. These critical remarks explain, why this technique never succeeded gaining wider acceptance for economic assessment.

Furthermore, inter-generation aspects may be considered in relation to the market system. This system fails to deal properly with externalities, designating effects in the exchange of goods and services that the market price reflects inadequately. The present environmental deterioration and irreversible depletion of natural resources suggest, that the interests of future generations must be considered, at least partly, as externalities.

As real interest rates are the outcome of the market system, it is questionable, whether they safeguard an adequate inter-generation distribution of resources [Samuelson 73:49; Lipsey 84:436; Baumol 88:643-6].

In this debate, some authors advocate discounting non-monetary health effects at lower rates [Parsonage 91]. This argument is based on the idea, that the utility of health improvements is independent of income and the moment of realisation. This view encourages counter-arguments. First, pure time preference is not related to income, although changing income expectations may alter the willingness to pay for the earlier command of goods and services. The relevant price depends simultaneously on the demand to advance the availability of goods or services and on the supply of financial assets to realise that demand. This observation may explain, why real interest rates are at present considerably higher than in the fifties and the sixties, although the growth rates of real incomes, as well as expectations of future growth rates, were at that time in most Western countries far more auspicious than in recent years. Consequently, the factor *"income"* seems immaterial to this argument.

Second, health care is merely one determinant of health, besides food, housing, clothing, articles for personal care, et cetera. Moreover, health is one of the factors that determine human welfare. In other words, the health care sector is part of a vast decision-making process. Although the health care sector differs considerably from other sectors regarding its structure, financing, and planning, it does not require a specific regime as to time preference. Moreover, time reference relates in this context to the product *care* and not to its production system. In so far as real interest rates provide information on time preference in general, they present indications on time preference related to health care. However, the time preference for a specific product may not coincide with the general time preference. The total demand for loans, created by the desire to advance the availability of goods and services, reflects a two-dimensional aggregation: per person and per product. Empirical data are not sufficiently detailed to differentiate real interest rates towards different products. Therefore, statements on differences between the general time preference and the time preference for a specific product are mere speculations.

The previous remarks cause uncertainty. Apparently, objective criteria provide insufficient support for reaching consensus on the discount rate. Nevertheless, previously cited publications indicate, that many economic evaluations of health care projects fix the discount rate at 5%. Elsewhere, a comparable uniformity is rather unusual, how-

ever[4]. For that reason, the results presented in part C, D, and E are discounted at three annual rates: 0%, 5%, and 10%. At the first rate, discounting does not affect the undiscounted results. The second rate approximates the present real interest rate. The third rate indicates the time preference expressed by the official discount rate of several countries during the seventies.

9.3 Marginal and Average Analysis

Several authors emphasise the importance of the marginal analysis, because it is the cornerstone in the economic theory of efficient allocation [Drummond 80:20-2, 100-1, 87:29; Guyatt 86; Blades 87; Eisenberg 89; Hodgson 89]. From mathematics, the marginal analysis borrows the technique of differentiation, which requires infinitely small variations. Like practical situations, the simulation fails to meet that condition. In this context, the marginal analysis is based on differences between two succeeding scenarios of ophthalmic care. The simulation calculates, for instance, the reduction of vision loss after intensifying ophthalmic care from scenario 2 to scenario 3. It also determines the increase in costs. The ratio of these two findings indicates approximately which financial resources are needed to reduce vision loss by one year. Scenario 0 is the basis of the average analysis. An example may illustrate this. The average costs for preventing one year vision loss in scenario 4 correspond to the quotient of two numbers: (1) the costs of ophthalmic care in scenario 4 and (2) the difference between total vision loss in scenario 0 and scenario 4.

In other words, the simulation facilitates both the marginal and the average analysis, although the former is open to criticism. The marginal analysis could easily be ameliorated by increasing the number of scenarios. This enables analysing smaller variations to bring the analysis in closer agreement with the rules of differentiation. For two reasons, the simulation does not implement this improvement. (1) Numerous patients fail to follow the recommended frequency of ophthalmic examinations. Clearly structured schemes of ophthalmic examinations may encourage compliance. They demand time intervals that patients can remember and respect easily, like a year or half a year. This requirement restricts the number of alternatives. (2) As a rule, simulations generate more alternatives than *"classical"* investigations. Consequently, simulations provide firmer ground for a marginal analysis.

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9.4 Market Prices and Willingness to Pay

This investigation expresses all costs and benefits in Dutch guilders (symbol *f*). Following common knowledge, total costs and benefits equal the product of prices and quantities. Previous chapters attempt to justify, how the simulation model determines quantities. In this chapter, subsequent sections want to legitimate the prices used in the analysis. Preliminarily, this section presents a general justification.

Ideally, *opportunity costs* constitute the nucleus of economic assessment. This concept relates to the fundamental issue of economics: the study of weighing alternatives given scarce resources. *Opportunity costs* equal the foregone benefits of the best alternative [Drummond 87:41; Baumol 88:36]. If all markets were perfect, market prices would truly reflect *opportunity costs*. Actually, no market is perfect, mainly as a result of market power imbalances, government intervention, entrance barriers, income differences, and imperfect information. Closing the gap between market prices and opportunity costs is a far too fundamental issue to be treated at the sideline of this investigation. Therefore, *opportunity costs* are left out of consideration.

If markets were perfect, they would nevertheless reveal substantial shortcomings. Prices present the observable outcome of individual behaviour. Therefore, they do not reflect externalities, relating to consequences of individual decisions for other individuals. A well-known example in health care is the general reduction of contamination risks, after one single person is vaccinated against contagious diseases. To determine the money value of these consequences, the *willingness to pay* was measured by interviews. Persons were asked how much they would be prepared to pay for specific health effects [Avorn 84]. However, this technique invokes critical notes. First, the *willingness to pay* depends on income. Consequently, preferences of richer people have more weight than those of poorer people. Second, it is doubtful whether the answers reflect the actual *willingness to pay*.

Some investigators try to avoid this discrepancy by deriving *revealed preferences* from observed behaviour. For that purpose, they study expenses for other goods or bonuses for unhealthy or hazardous labour. The indirect nature of these calculations limits the precision of results. Moreover, this technique is hardly applied in the domain of ophthalmology, perhaps because contagious eye diseases are at present absent in industrialised countries. As it is doubtful, whether this approach masters the difficulties in determining the *willingness to pay*, this concept is left out of consideration. The money value of costs and benefits will therefore be based on market prices or care charges.

9.5 Human Capital Approach and Friction Costs

Economic evaluations of health care projects distinguish direct and indirect costs. The first category accommodates (1) medical costs for prevention, screening, and treatment, (2) costs borne by patients or their relatives, like expenditures on travel, special diets, clothing or housing, and (3) costs mentioned in the previous category but borne by the public sector or health care insurers. Indirect costs include production losses caused by morbidity, disablement, or premature mortality [Drummond 87:22]. This section presents some remarks on indirect costs. Direct costs are discussed in subsequent sections of this chapter.

Measuring production losses is a subject of controversy. Well-known is the *human capital approach*. This technique is based on the economic valuation of machines. Their net present value equals the balance of all discounted expected future benefits and costs. Machines should be replaced, when their net present value becomes inferior to that of new machines. This method raises resistance, not only because it seems to analyse people like machines, but also because it tends to overestimate benefits and losses, as the next paragraph explains. Furthermore, the results are quite sensitive to fluctuations of the discount rate. Finally, this technique favours younger persons and people with higher incomes. Hence, it may justify decisions that are detrimental to economically weaker citizens. According to the *human capital approach*, the productivity value of male employees in the United States equals 1.5 to 2 times the productivity value of female employees at nearly all ages [Hartunian 81:50].

Usually, the *human capital approach* equates production losses to cumulative potential earnings or production values. If a fully able employee becomes completely disabled, production losses equal the discounted value of the total potential production that the employee might have realised without disablement until the age of retirement. The disablement of young and highly qualified employees may generate huge production losses, according to this approach. However since the first oil crisis in 1973, most industrialised countries face substantial unemployment. Now, the labour supply can quickly fill gaps resulting from morbidity, disablement, or precocious mortality. This situation raises the question, whether cumulative potential production losses are a valid yardstick of actual production losses. In a recent publication, Koopmanschap and Van Ineveld advocate the technique of friction costs [92]. It confines losses to the friction period, covering the time needed to replace withdrawn employees. According to their calculations for patients with cardiovascular diseases, friction costs equal roughly a tenth of the production losses determined by the *human capital approach*. This new

method reduces the likelihood of overestimating production losses. However, it also invites critical notes.

So far, friction costs calculations concern paid labour only. They are directly related to existing age and gender specific gross-labour incomes. Consequently, friction costs broadly confirm the actual income distribution. In the Netherlands, the present average duration of the friction period is 2.5 months [Koopmanschap 92]. For the time being, empirical details on the relationship between the unemployment rate and the length of the friction period are unavailable, although deductive considerations suggest a negative correlation. In this first study, the friction period has a uniform length. It disregards differences in age, gender, profession, function, or region. Replacing highly educated and specialised persons may require longer friction periods, while increasing the relative weight of these persons in the total production losses. This differentiation could arouse opposition, like the differences in productivity value between American males and females mentioned previously with respect to the *human capital approach*. Finally, friction costs calculations ignore losses of expertise. By the end of the friction period, the vacancy is filled and the production losses stop immediately, although newly appointed employees may need months, or even years, to acquire the expertise of their predecessors.

The scope of the present investigation precludes comparing these evaluation techniques in depth. This may explain, why the simulation evades choosing and why it determines indirect costs by both techniques. The *human capital approach* is included for its widespread use in economic evaluations. The *friction costs technique* is applied, because it offers a promising alternative that may prevent excessively high estimates of production losses. That is quite relevant in this context, because ophthalmic care repels blindness as well as production losses. The simulation assesses reductions in production losses by comparing production losses in different scenarios. A technique that tends to overestimate the absolute level of production losses per scenario, contributes to overestimating differences of production losses between several scenarios. In other words, such a technique may ultimately overestimate the reduction of production costs enabled by ophthalmic care as well as the ensuing benefits. Apart from data by Koopmanschap and Van Ineveld, there are hardly any statistics on friction costs. The simulation must therefore recur to rough approximations, that section 11.7 and 14.7 will specify. Nevertheless, this technique will turn out to be a powerful instrument for criticising the results of the simulation.

9.6 Costs

According to the demarcation of this study, the analysis of medical costs is confined to ophthalmic examinations, fluorescein angiograms, and laser treatments. The simulation generates data on physical units. Following previous remarks, these physical units are transformed into monetary units by market prices or health care charges. At present, an investigation in the Academic Hospital of Maastricht tries to establish the cost prices of numerous procedures and operations by various medical specialisms. Results regarding ophthalmic care have not been published yet. The lack of further statistics on this issue may explain, why there is no consensus in the Netherlands on cost prices of ophthalmic care. Consequently, evidence for determining market prices fails. The simulation must therefore recur to medical charges. It uses the statistics presented in table 9.2. Recently, official charges were reduced by some 10% to 20%. This decrease would lead to more favourable ratios of costs and effects.

	Private health insurance		Social health insurance	
	Ophthalmologist	Hospital	Ophthalmologist	Hospital
Ophthalmoscopy	*f* 45.50	*f* 17.20 per year	*f* 43.-- per year	---
Fluorescein angiography	*f* 159.--	*f* 181.60	*f* 117.--	*f* 181.60
Photocoagulation	*f* 599.--	*f* 950.-- per year	*f* 400.-- per year	*f* 950.-- per year
charges in Dutch guilders (*f*) per screening visit or treatment unless stated otherwise				

Table 9.2 - Ophthalmic care charges in the Netherlands (1992)[5]

In 1987, some 62% of the total population in the Netherlands received social health insurance through compulsory membership in sickness funds, approximately 32% had private health insurance, and some 6% were beneficiaries of statutory health insurance schemes for public servants [Elsinga 89:A.3-6-9]. For the last group, specific statistics on the prevalence of DM and ophthalmic care charges are sporadic. Therefore, this group is left out of consideration. Social health insurance covers the medical expenses for the recipients of social insurance benefits and for persons whose annual income is inferior to a statutory ceiling (1991: *f* 52,300). Consequently, privately insured persons have, on average, substantially higher incomes than socially insured persons. DM

5 These charges are based on two publications by the Dutch Central Office on Health Care Charges: *"Partikuliere tarieven medisch-specialistische hulp"* and *"Honorering specialistische hulp door ziekenfondsen"*, Utrecht, 1992. The calculations were performed by Mrs. A. Ruys and Mr. W. Meurs, Division Production and Invoicing, Financial Department, Academic Hospital Sint Radboud, Nijmegen. Herewith, I acknowledge my gratitude for their kind and important help.

remains a rather severe mental and physical burden, despite important improvements in medical technology. Hence, diabetic patients have to face specific career handicaps, that may worsen income perspectives. The simulation presumes therefore that the average income of diabetic patients is inferior to that of the general population. This implies that comparatively more diabetic patients receive social health insurance. In the absence of reliable statistics, the simulation presumes that 75% of all diabetic patients have social health insurance and 25% private health insurance. Most ophthalmologists practice autonomously in single-speciality groups at hospital clinics and polyclinics. Table 9.2 indicates that private and social health insurance charges are split to cover ophthalmic practice costs and costs of hospital facilities separately.

Ophthalmic examinations and treatments generate (production) time costs besides medical costs. In the Netherlands, time costs are borne by patients, employers, health care insurers and social security funds. These costs are comparatively insignificant and widely spread. Therefore, they are unlikely to be sizeable determinants of policy decisions on ophthalmic care. Moreover, statistics on time costs are scarce. The simulation leaves these costs out of consideration. The previously mentioned medical costs belong to the category *direct costs* [Drummond 87:22].

9.7 Effects and Benefits

For reasons presented in section 9.1, the simulation uses physical units to quantify the effects of ophthalmic care, namely the reduction of visual impairment. It calculates yearly statistics on the absolute prevalence of blindness and moderate vision (visual acuity in the better eye <0.5 or 20/40). Furthermore, it presents additional details by classifying eyes in 10 visual acuity categories: (1) 0.0 to 0.1, (2) 0.1 to 0.2, ... (10) 0.9 to 1.0.

The simulation examines the following benefits of ophthalmic care: savings in (1) production losses and (2) facilities provided for disabilities, including optical expedients. These savings should be considered as indirect and direct benefits, respectively. Production losses are determined by the two techniques introduced in section 9.5. They both require statistics on labour productivity specified according to visual acuity, age, gender and function. Because there is a lack of reliable empirical findings, several investigators use gross wages as a substitute, including social security premiums paid by employers [Drummond 80:30, 87:79; Hartunian 81:47-56; Blades 87]. Subsequently, they estimate the effect of vision savings on labour productivity by a factor ranging from 0 to 1, both values included. The total production gains equal the gross

monthly wage rate multiplied by this factor and by the duration of these gains expressed in months. This phase of the calculation highlights differences between the *human capital approach* and the *friction costs technique*.

Which wage rate should be the basis of the simulation? Following the previous argumentation, this issue offers more uncertainty than certainty. The selection of existing gross monthly wage rates confirms the actual income distribution and tends to degrade lower rank work, volunteer activities, and unpaid household work. This is detrimental to the social status of women, old-age pensioners, and unemployed or disabled persons. However, a legitimate and socially more acceptable choice would require a separate investigation. This makes an approximation unavoidable. It should (1) broadly correspond with the actual valuation of paid labour, (2) respect the position of housekeepers, old-age pensioners and other economically non-active persons, and (3) avoid excessive estimates of savings in production losses.

A rough approximation ignoring individual features seems hardly suitable. The primary income distribution which reflects the prices of production factors before the payment of income taxes and the receipt of social security allowances, reveals considerable spread as a result of substantial differences in productivity. It justifies a differentiated approximation using data on primary incomes for measuring the labour productivity of economically active persons. However, the relationship between primary incomes and labour productivity is ambiguous. Moreover, a differentiated approximation should also quantify the contributions of economically non-active persons adequately and in a proper proportion to the contributions by the economically active population. The sparseness of empirical findings renders this quantification speculative.

A differentiated approximation seems no more defensible than a rougher approach. Nonetheless, the simulation wants to present an impression of production losses. As a differentiated approximation might erroneously create an illusion of certainty, the simulation opts for a global approximation based on a specific average value of labour productivity. This approach is transparent by its simplicity. Moreover, the reader can adjust the basis of this approximation rather easily by selecting another average value of labour productivity. Then, the results regarding savings in production losses should be multiplied by a factor that equals the quotient of the new and the original basis.

Age of onset DM (years)	15	35	55	75
Average labour productivity per year	ƒ 75,000	ƒ 60,000	ƒ 45,000	ƒ 30,000

Table 9.3 - Presumed average labour productivity (1992)

According to Dutch National Income Accounts, the average domestic product per labour year (gross; factor costs) equalled *f* 91,430 in 1990 [CBS 60..92, 92:362]. This amount may well be a reliable estimate of the average yearly labour productivity of full-time employees and self-employed persons. According to table 9.3, the simulation adjusts that amount downward to *f* 75,000 per year for IDDM patients. This correction is based on the following considerations. (1) The marginal labour productivity is usually smaller than the average labour productivity. (2) Generally, old-age pensioners and economically non-active persons are less productive than economically active persons. Table 9.3 reveals furthermore, that an increase in the age of onset of DM is associated with a decrease of the average labour productivity. This has the following reason. As the age of onset in a cohort rises, visual impairment resulting from DR is concentrated at older ages. Consequently, potential savings in production losses decrease.

$$Q^{c}_{t,s,p} = [1 - (1 - v^{c}_{t,s,p})^{2}]\, Q_{max} \quad \{v^{c}_{t,s,p} \in \mathbf{R} \mid 0 \le v^{c}_{t,s,p} \le 1\} \qquad (9.3)$$

In equation 9.3, a second-degree function represents the presumed relationship between the maximum labour productivity Q_{max}, visual acuity $v^{c}_{t,s,p}$ (of the better eye), and the actual labour productivity $Q^{c}_{t,s,p}$ regarding scenario c, period t, gender s, and patient p. The marginal yearly savings on production losses equal $Q^{c}_{t,s,p} - Q^{c-1}_{t,s,p}$ and the absolute yearly savings on production losses $Q^{c}_{t,s,p} - Q^{0}_{t,s,p}$ $(c > 0)$. For IDDM patients, figure 9.1 presents the average labour productivity as a function of visual acuity at statistics for 1990.

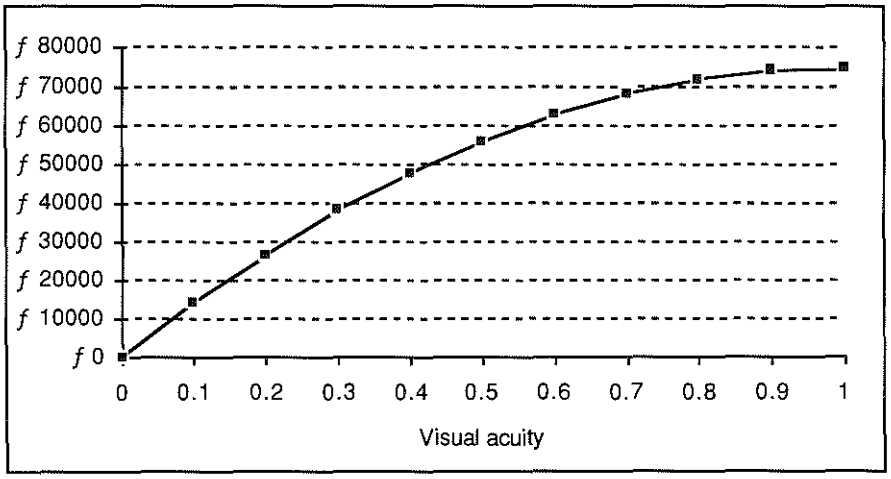

Figure 9.1 - Visual acuity and average labour productivity (age of onset 15 years)

The second category of benefits is now presented: savings in disability facilities including optical expedients. The concept *disability facilities* has a wider meaning and embodies home adjustment, information, advice, support, revalidation, instruction, training, and transportation. In the Netherlands, numerous organisations are specialised in supplying subsets of these facilities in accordance with distinct individual needs. The following sources of financing can be distinguished: (1) income related premiums with respect to the *Exceptional Medical Expenses Act (AWBZ)*; (2) social insurance contributions concerning the *Labour Disability Insurance Act (WAO)* and the *General Labour Disability Act (AAW)*; (3) social insurance contributions to sickness funds; (4) premiums of private health care insurance based on altruistic risk sharing, pure ex-ante risks or a mixture of both extremes; (5) direct payments; (6) gifts; (7) subsidies. Moreover, the Dutch Government safeguards the interests of visually impaired persons by additional legislation and regulation.

The diversity of supply, demand, financing, legislation and regulation makes the domain of disability facilities rather heterogeneous and little transparent. This hinders the charting of costs and explains the shortage of aggregate data [Stoevelaar 92:59]. Filling these gaps would require research well beyond the borders of the present study. Therefore, the next paragraphs present solely the most important and costly facilities reimbursed by the Government, industrial social funds, the *General Civil Servants' Pension Fund (ABP)*, sickness funds, private health care insurers, and private foundations. The amounts mentioned below are mere indications of actual prices[6].

Reimbursement for home adjustment is usually confined to one adapted lighting unit (*f* 600). Single persons may claim funds for another similar lighting unit in the kitchen. Expensive adjustments, like sun-blinds or heavy curtains, are unlikely to be remunerated. In 1992, the *Exceptional Medical Expenses Act* allocated *f* 43 million to finance information, advice, support, revalidation, instruction, training and transportation. These funds reached about 5,000 patients. However, the Netherlands counts some 60,000 to 120,000 visually impaired persons who may request financial support in the framework of this act. Many patients seem unaware of their rights and fail to claim funds. Other patients do not want special facilities, because they rather do not admit their handicap. After these remarks, it may appear reasonable to fix the average amount at *f* 2,000 per patient per year. This sum covers all these facilities.

6 This approach is based on comprehensive suggestions by Mr. P.A.M. Hendriks (Director Financial Department, Visio, Huizen), J.A. Welling M.A. (General Director, Visio, Huizen) and B. Wouters M.A. (Psychologist, het Loo-Erf, Apeldoorn). Herewith, I acknowledge my gratitude for their crucial and most valuable help.

Numerous patients receive reimbursement for the following aids: spectacles with prism magnifiers (*f* 1,500 to *f* 2,000), television magnifying-glasses (*f* 7,000), and memo tape recorders (*f* 200). The average annual outlay on optical aids depends on vision stability. Because unstable vision is quite typical of DR, the optical expedients of diabetic patients need to be replaced or readapted frequently. Visually impaired persons may also claim funds for an ordinary typewriter (*f* 500) to contact in writing persons without visual impairment. Moreover, many blind persons receive full reimbursement for a Braille typewriter (*f* 2,000). Some 800 blind persons have a guide-dog, whose training and adaptation cost some *f* 25,000. For maintaining social contacts, visually impaired persons may declare taxi rides up to an annual maximum. According to conservative estimates, annual charges equal on average at least *f* 2,000 for blind persons and some *f* 1,000 for other visually impaired persons. Besides, the costs of trips with medical or therapeutical motives are refunded completely. Libraries for the blind as well as sound tape mail and Braille mail are free of charge for the blind. Finally, somebody guiding a blind person in the public transportation system may travel gratuitously. The previously mentioned facilities mainly relate to a person's private life. Specific rules apply to the sphere of employment, where essentially all necessary adaptations are refunded.

Age of onset DM (years)	15	35	55	75
Costs of disability facilities per year	*f* 7,000	*f* 6,000	*f* 4,500	*f* 3,000

Table 9.4 - Presumed average costs of disability facilities (1992)

Table 9.4 presents the presumed average annual costs of disability facilities in case of complete visual impairment, corresponding to a vision of 0.0 in both eyes. Each amount is a conservative estimate of the previously mentioned costs of disability facilities plus optical aids. It is important to notice, that diabetic patients have to put up with severe visual impairment for far shorter periods than congenitally blind persons. This enlarges the average annual costs. At older ages of onset, less adjustments are needed in the sphere of employment, as well as fewer optical aids. However, these patients require more labour intensive care. Respecting these opposed movements, the maximum annual costs decrease rather slowly as the age of onset increases.

$$F^{c}_{t,s,p} = (1 - v^{c}_{t,s,p})^{8} F_{max} \quad \{v^{c}_{t,s,p} \in \mathbf{R} \mid 0 \le v^{c}_{t,s,p} \le 1\} \qquad (9.4)$$

Equation 9.4 presents a function of degree eight to formalise the relationship between the maximum annual costs of disability facilities F_{max}, visual acuity $v^{c}_{t,s,p}$ (of the better eye) and the actual annual costs of disability facilities $F^{c}_{t,s,p}$ for scenario c, period t, gender s, and patient p. The marginal annual savings in disability facilities equal

$F^{c-1}_{t,s,p} - F^{c}_{t,s,p}$ and the absolute annual savings $F^{0}_{t,s,p} - F^{c}_{t,s,p}$ ($c > 0$). For IDDM patients, figure 9.2 presents the relationship between visual acuity in the better eye and the average annual costs of disability facilities, as revealed by statistics for 1990.

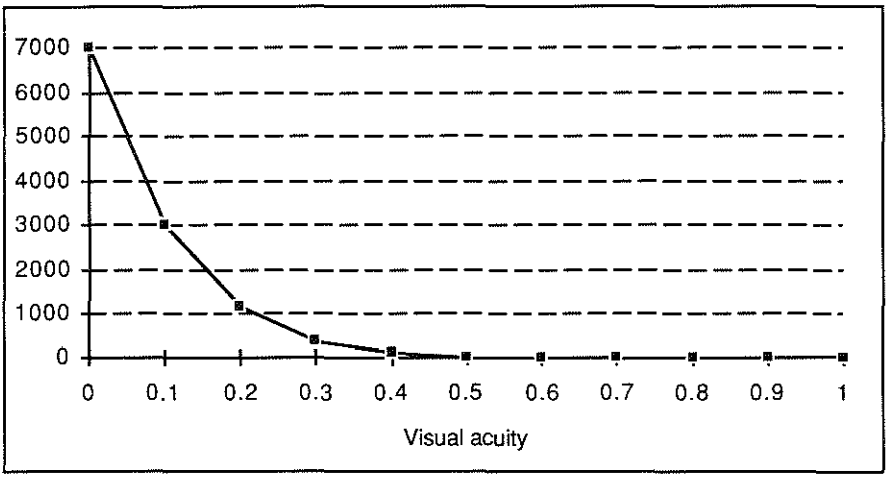

Figure 9.2 - Visual acuity and average costs of disablement faciliites

After this introduction to the main characteristics of the simulation, part C and part D will present the results for IDDM and NIDDM patients respectively.

C

Insulin-Dependent Diabetes Mellitus

10

Epidemiologic Data

10.1 Introduction

Prior to the presentation of the main results for IDDM patients in the next chapter, the following sections provide information on the epidemiologic data that constitute the base of the simulation. This survey may be considered as a further specification of table 3.2 in section 3.7. It treats DR, ME, PDR, visual impairment, and blindness, successively.

10.2 Diabetic Retinopathy

Table 10.1 represents key statistics taken from three epidemiologic studies on the prevalence of DR, including ME and PDR. These investigations did not reveal significant differences related to gender. However, they demonstrated unambiguously, that the prevalence rates of DR depend principally on the duration of IDDM.

Number of years since onset of IDDM	[Palmberg 81] (N = 461) Washington United States	[Klein 84b] (N = 996) Wisconsin United States	[Klein 89c] (N = 996) Wisconsin United States
5	—	17%	—
7	50%	—	—
15	—	97.5%	—
17-50	90%	—	—
20	—	—	97%

Table 10.1 - Prevalence rates of DR for IDDM patients

An investigation by Dwyer and co-workers [85] uncovered lower prevalence rates of DR: 20% after 8 years IDDM and 65% after 18 years IDDM. These findings are left out of consideration for three reasons. (1) They relate to 75 IDDM patients. (2) They differ significantly from the data presented by the three publications in table 10.1. These findings are characterised by a striking mutual harmony. (3) Many publications refer to the results by Klein and associates [e.g. Krolewski 87; Javitt 89, 90, 91; L'Esperance 90:667; Dasbach 91; STG 91:44-5].

10.3 Macular Edema

Again, an investigation by Klein and co-workers provides the firmest ground [84f]. The statistics in table 10.2 originate from that investigation. They reflect prevalence rates by age rather than by duration of IDDM.

Age	Number of patients	Prevalence of ME
0-14	105	0.0%
15-19	153	2.0%
20-29	257	12.8%
30-44	216	14.8%
≥ 45	88	26.1%

Table 10.2 - Prevalence rates of ME for IDDM patients [Klein 84f]

However, this investigation states that the duration of IDDM is the principal determinant of ME. A graph in this publication shows, for instance, that the prevalence rate of ME may reach 33% for patients who suffer from IDDM for twenty years or longer. Furthermore, the prevalence of ME exceeds 40% after 40 years of IDDM in the simulation by Javitt et al. [89].

10.4 Proliferative Diabetic Retinopathy

Table 10.3 presents key figures from studies by Palmberg et al. and Klein et al.

Number of years since onset of IDDM	[Palmberg 81] (N = 461) Washington United States	[Klein 84b] (N = 996) Wisconsin United States
< 5	—	0%
10	—	4%
< 13	0%	—
15	—	25%
26	26%	—
35	—	67%

Table 10.3 - Prevalence rates of PDR for IDDM patients

According to the publication by Klein and associates, the prevalence rate of PDR decreases gradually for patients who have lived with IDDM for more than 35 years. The article does not illustrate this statement by figures. However, a graph indicates that the prevalence rate falls to some 40% fifty years after the onset of IDDM. Presuming that regression rates of DR are negligible, it seems plausible to explain this phenomenon as follows. Thirty-five or more years after the onset of IDDM, the presence of PDR raises mortality risks significantly, whereas the incidence of PDR is rather limited.

Nevertheless, the simulation ignores this reduction in the prevalence of PDR for the following reason. Only 10.0% (N = 100) of the study population were subject to IDDM for more than 30 years. The article does not specify the number of patients, who had IDDM for more than 35 years. However, it seems quite certain, that the reduction in the prevalence of PDR was observed in a rather small study group. Moreover, the article mentions this phenomenon only in passing, which may indicate that the investigators doubt the trustworthiness of this observation. The study by Klein and co-workers confirms broadly the earlier findings by Root and associates [59]. This investigation revealed the following prevalence rates for patients who develop IDDM before the age of fifteen and who live twenty years or longer after the onset of IDDM: age 20-29 years 28.7%; age 30-39 years 53.1%; age 40-49 years 58.4%.

10.5 Visual Impairment

Like other investigations [Davis 79; Klein 84e; Herman 90], the simulation fixes the upper limit of visual impairment at 0.5, or 20/40, in the better eye. Visual impairment comprises moderate vision and blindness, as specified by table 7.3 and table 7.4 in secion 7.3. Statistics on the prevalence of this disorder are rather scarce. Again, a

study in the American state Wisconsin by Klein and associates offers support [84e]. The first five columns of table 10.4 borrow key figures from this study. The last two columns present results of our own crosstabulation analysis based on the four preceding columns. Considering the values of χ^2, the differences between females and males are not nearly significant. This crosstabulation analysis is confined to visual impairment, because the consulted publications do not provide sufficient data for similar analyses of other disorders.

	Females		Males		(own) Crosstabulation females by males	
Age	Number of patients	Prevalence of vision ≤ 20/40 in better eye	Number of patients	Prevalence of vision ≤ 20/40 in better eye	Pearson χ^2	Significance
0-17	87	2.3%	110	3.6%	0.2943	0.5875
18-24	123	4.9%	113	3.5%	0.2599	0.6102
25-34	138	5.8%	151	8.6%	0.8462	0.3576
35-44	66	10.6%	71	12.7%	0.1421	0.7062
45-54	40	17.5%	39	23.1%	0.3803	0.5375
≥ 55	30	26.7%	28	21.4%	0.2170	0.6413

Table 10.4 - Prevalence rates of visual impairment for IDDM patients [Klein 84e]

According to the simulation by Javitt et al., the prevalence rate of peripheral vision loss exceeds 50% at the age of 57 years or 44.5 years after the onset of IDDM, while the prevalence rate of central acuity loss then surpasses 30% [89]. These results do not harmonise with the data in table 10.4. As the simulation is designed to achieve justifiable forecasts of the effects of ophthalmic care, it chooses data closer to the empirical findings of Klein and associates. The latter accord with an earlier study of 307 IDDM patients from 1933 to 1973 by Deckert and co-workers [78]. They found prevalence rates of visual impairment (= unable to read the daily paper without a magnifying glass) to culminate at 30.6% for patients who had survived some 36 years on average after the diagnosis of IDDM.

10.6 Blindness

The simulation borrows key statistics from a study by Klein et al. which are presented in table 10.5. This investigation did not reveal significant gender-specific differences. According to the investigation by Deckert et al. [78], mentioned in the previous section, the maximum prevalence rate of blindness equals 16.3%.

Number of years since onset of IDDM	[Klein 84e] (N = 996) Wisconsin United States
15-19	3%
≥ 30	12%

Table 10.5 - Prevalence rates of blindness for IDDM patients

Oosterhuis [84] states, that in the absence of laser treatment 50% to 75% of the patients become blind within five years after the onset of PDR and 100% within ten years. A study of American patients revealed that 43% became blind within five years after the onset of PDR [Caird 69, cited by L'Esperance 90:667]. By associating these findings with the prevalence rates in table 10.3, it becomes obvious that the prevalence rates of blindness should be considerably higher than 12% forty years or more after the onset of IDDM. According to table 10.3, the prevalence rate of PDR equals 67% thirty-five years after the onset of IDDM. Following the most auspicious statistics by Caird and Oosterhuis, 43%, or 29% of all patients are blind five years later. The latter percentage, 29%, requires a downward correction for mortality differences between patients with and without PDR. The available data do not provide sufficient support to determine this correction exactly.

Number of years since onset of IDDM	Number of survivors in cohort of 10,000 male IDDM patients	Number of patients without PDR	Number of patients with PDR	Number of blind patients
35	7005	2312	4693	0
40	5653	2312	3341	1437

Table 10.6 - Results of a crude calculation for IDDM patients

As an alternative, table 10.6 presents the results of a crude calculation. The number of surviving males is taken from the simulation results for scenario 0 (no ophthalmic care). If the prevalence rate equals 67%, 4,693 of the 7,005 male patients have developed PDR 35 years after the onset of IDDM. Assuming that no patient without PDR dies or develops PDR within the next five years, the number of patients with PDR equals 3,341 forty years after the onset of IDDM, in the absence of regression. Of these patients 43%, or 1,437, are blind. Then, the prevalence rate of blindness exceeds 25% (≈ 1,437 / 5,653), if no patient were blind 35 years after the onset of IDDM. Obviously, all phases of this crude calculation start from extreme assumptions, that

minimise the occurrence of blindness. Consequently, the actual prevalence rate may be substantially higher than 25%.

Nonetheless, the simulation limits the prevalence of blindness to some 12% during the first 60 years after the onset of IDDM. In subsequent years, the number of survivors is too small to obtain reliable results. For the same reason, those years have a negligible impact on the overall results. Thus, the simulation estimates the occurrence of blindness in the absence of ophthalmic care conservatively, although higher prevalence rates might appear justifiable. This strategy aims at promoting the credibility of results by avoiding the overestimation of effects.

10.7 Summary of Prevalence Rates

Table 10.7 presents the prevalence rates of retinal disorders and visual impairment that apply to the simulation for IDDM patients.

	After 15 yr IDDM	Maximum
DR	98%	98%
ME	15%	33%
PDR	25%	67%
≤ 20/40	14%	35%
Blindness	3%	12%

Table 10.7 - Prevalence rates of retinal disorders and visual impairment

The results in the following chapter originate from these prevalence rates.

11

Results

11.1 Introduction

Succeeding sections present the principal outcomes of the simulation for IDDM patients. The results may be divided into three groups. The first group includes epidemiologic findings: (a) the life expectation of diabetic patients compared to the general population and (b) the prevalence of DR, ME, PDR, visual impairment and blindness in different scenarios. These results enable one to express the effectiveness of ophthalmic care in reductions of visual impairment. The second group comprises data on the volume of ophthalmic care in different scenarios, specified by the number of ophthalmic examinations, fluorescein angiograms and laser treatments. The third group relates to economic assessment. It comprises (a) direct costs, (b) effects and benefits, and (c) average and marginal analyses. The simulation distinguishes two options of ophthalmic care, α and β, that were introduced in section 8.8. This chapter presents the results of option α only, unless the two options generate quite different results.

11.2 Life Expectation

Table 11.1 compares the life expectation of IDDM patients to that of the general population in the Netherlands for persons reaching the age of 15 years. The comparison is based on hazard rates for 1983 to 1987 [CBS 88b:44-5]. According to the simulation, IDDM shortens the life expectation by almost a third, which is marginally more auspicious than the reduction of one third mentioned by the STG [91:30, 87]. This moderate optimism seems justifiable, because the relative life expectation of IDDM patients - as compared to the general population - has increased steadily since 1921, when Banting and Best succeeded in producing an insulin extract. This trend is likely to persist in the near future: (1) Improved outpatient diabetes education is making patients more knowledgeable and co-operative in controlling IDDM by self-monitoring, insulin injections,

diets and living style adaptation [Kaplan 86; Kemenade 90]. (2) Instruments for self-management have become more sophisticated, easier to use, and less expensive. Consequently, a relatively larger number of patients possess more advanced devices for controlling IDDM. (3) Modern medical technology offers superior treatment of chronic complications. Furthermore, the simulation depicts future consequences of distinct scenarios of ophthalmic care during a period reaching beyond the year 2050. Finally, the results of the simulation are the basis of a prognosis until the year 2030. The percentages in table 11.1 represent the quotient of the life expectation for diabetic patients and the general population.

			Females		Males	
General population		p	65.50	100.00%	59.06	100.00%
IDDM-patients	Scenario 0	s0	44.77	68.34%	41.38	70.07%
	Scenario 1	s1	45.82	69.95%	42.00	71.11%
	Scenario 2	s2	45.96	70.16%	42.44	71.87%
	Scenario 3	s3	46.23	70.58%	42.47	71.92%
	Scenario 4	s4	46.20	70.53%	42.33	71.68%

Table 11.1 - Life expectation at the age of 15 years ; option α

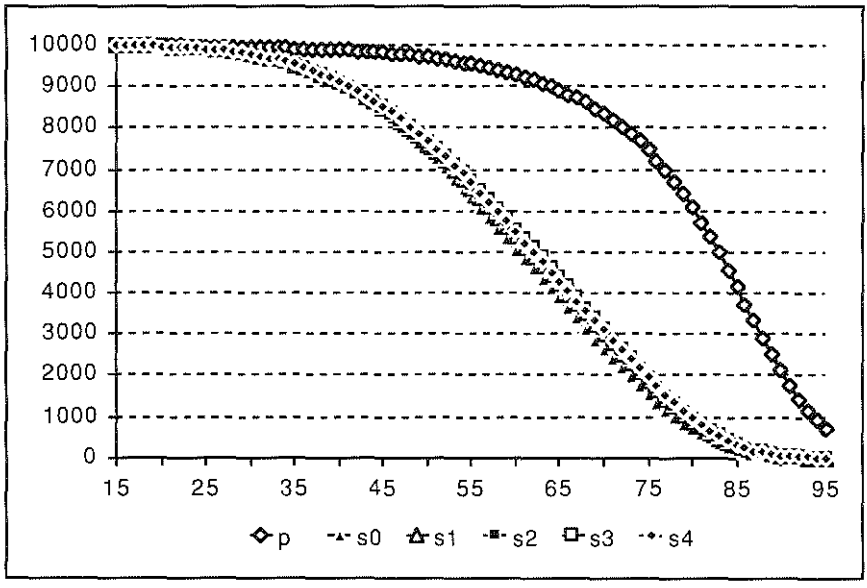

Figure 11.1 - Number of surviving females by age (years); option α

The numbers in table 11.1 are derived from the statistics represented graphically by figure 11.1 and figure 11.2. In these graphs, the curves concerning the general population illustrate life table data published by the CBS [88b:44-5]. The five remaining curves are the outcome of the simulation. Ophthalmic care benefits the life expectation of IDDM patients, although the effects are rather insignificant. Setting the percentages for s0 versus s1, s2, s3, and s4 reveals, that female patients profit relatively more than male patients. Women enjoy the effects of successful laser treatments longer than men because of their higher life expectation. Hence, they may avoid higher hazard rates resulting from retinal deterioration and visual impairment, during a longer period. In both figures, the horizontal axis represents the age, whereas the vertical axis indicates the number of survivors.

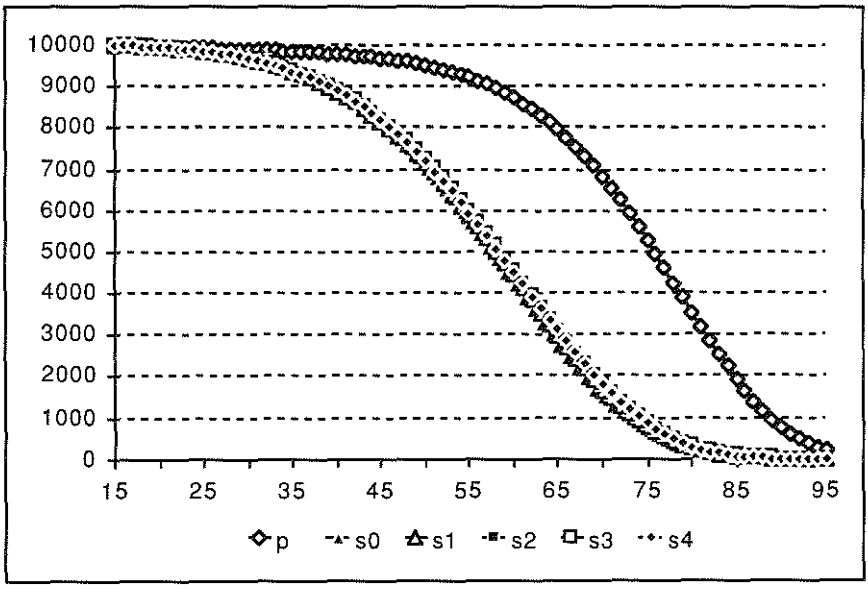

Figure 11.2 - Number of surviving males by age (years); option α

11.3 Prevalence of DR, ME, PDR, Visual Impairment and Blindness

For s0, the scenario without ophthalmic care, figure 11.3 and figure 11.4 picture the prevalence rates of DR, ME, PDR, visual impairment and blindness, by age. The curves reveal no significant gender-specific differences. At the age of 35, or 20 years after the onset of IDDM, virtually all patients suffer from DR. Only few patients younger than 30 years develop ME or PDR but thereafter prevalence rates rise sharply, principally of PDR. Prevalence rates stagnate for patients older than 50 years.

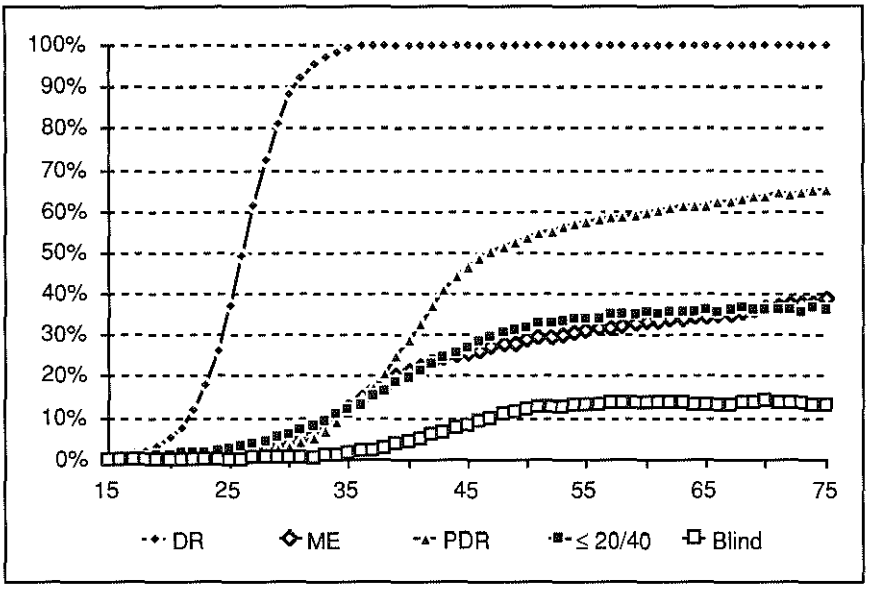

Figure 11.3 - Relative prevalence of retinopathy and visual impairment for females by age (years); scenario 0; option α

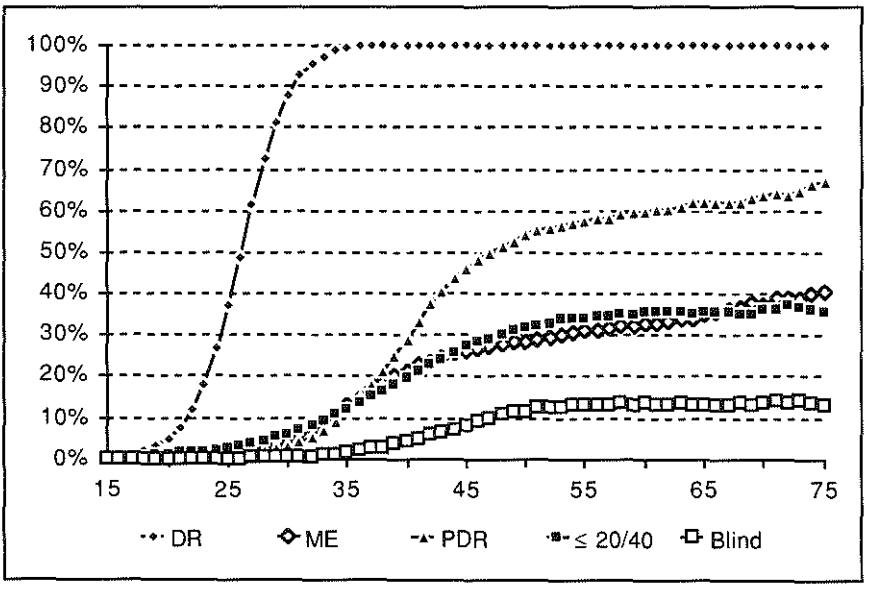

Figure 11.4 - Relative prevalence of retinopathy and visual impairment for males by age (years); scenario 0; option α

The prevalence rates of visual impairment (≤ 20/40 in better eye) correspond closely to the prevalence rates of ME. Blindness is nearly absent before the age of 35 years. In the next 15 years, the prevalence rates of blindness increase steadily. They stabilise near their maximum for patients older than 50 years.

Figure 11.3 and figure 11.4 reflect three distinct movements in time. At first, virtually all patients develop DR. Some 10 to 15 years later, many patients have to face PDR or ME. The prevalence rate of visual impairment gradually approaches its maximum, simultaneously. Finally, another 5 to 10 years later, a considerable number of patients with PDR or ME becomes blind.

Figure 11.5 and figure 11.6 represent the absolute prevalence for female and male patients respectively in cohorts including 10,000 patients, initially. The curve for DR indicates the number of survivors at ages over 35 years, because approximately all patients then suffer from DR. The prevalence of blindness does not gain importance, until a considerable number of patients have passed away. This limits the absolute prevalence of blindness.

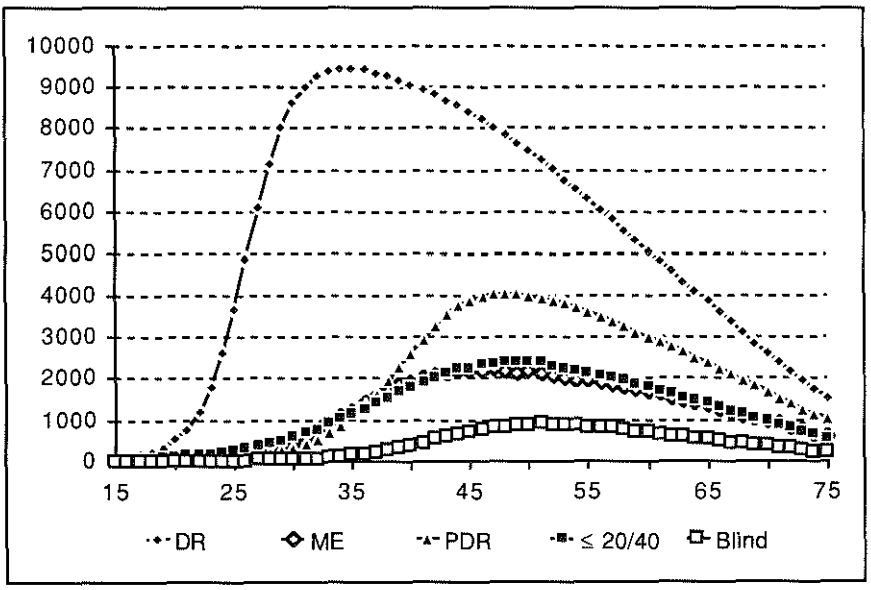

Figure 11.5 - Absolute prevalence of retinopathy and visual impairment for females by age (years); scenario 0; option α

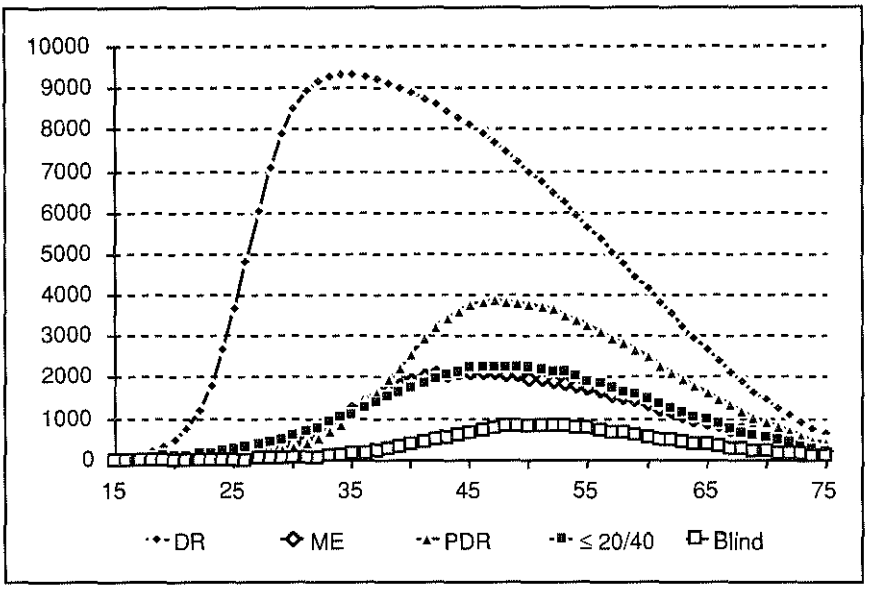

Figure 11.6 - Absolute prevalence of retinopathy and visual impairment for males by age (years); scenario 0; option α

	Females		Males	
s0	24529	100.00%	20100	100.00%
s1	19341	78.85%	15653	77.87%
s2	14852	60.55%	12472	62.05%
s3	12788	52.13%	10873	54.09%
s4	11860	48.35%	10191	50.70%

Table 11.2 - Cumulative prevalence of blindness (years and % of s0); option α

Table 11.2 expresses the cumulative prevalence of blindness in years, for five scenarios and by gender. In the absence of ophthalmic care, female patients are on average nearly 2.5 years blind and male patients over 2.0 years. Ophthalmic care reduces the prevalence of blindness substantially, maximally by 51.65% for female patients in s4 as compared to s0. According to table 11.2, ophthalmic care has diminishing marginal returns. From s0 to s1, the reduction of blindness is considerably more important than from s1 to s2, although both scenario changes cause comparable volume changes in ophthalmic care. The diminishing marginal effect of ophthalmic care is most obvious between s3 and s4.

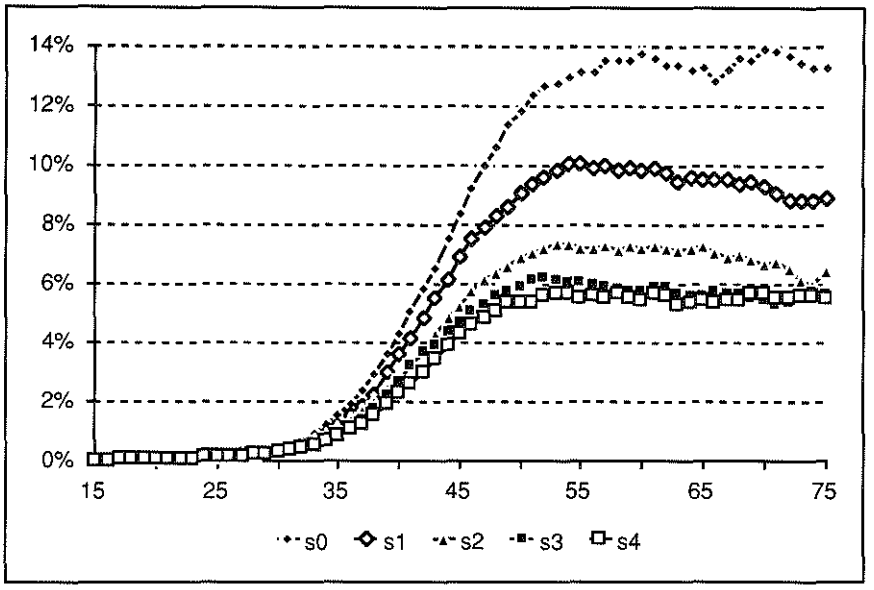

Figure 11.7 - Relative prevalence of blindness for females by age (years); option α

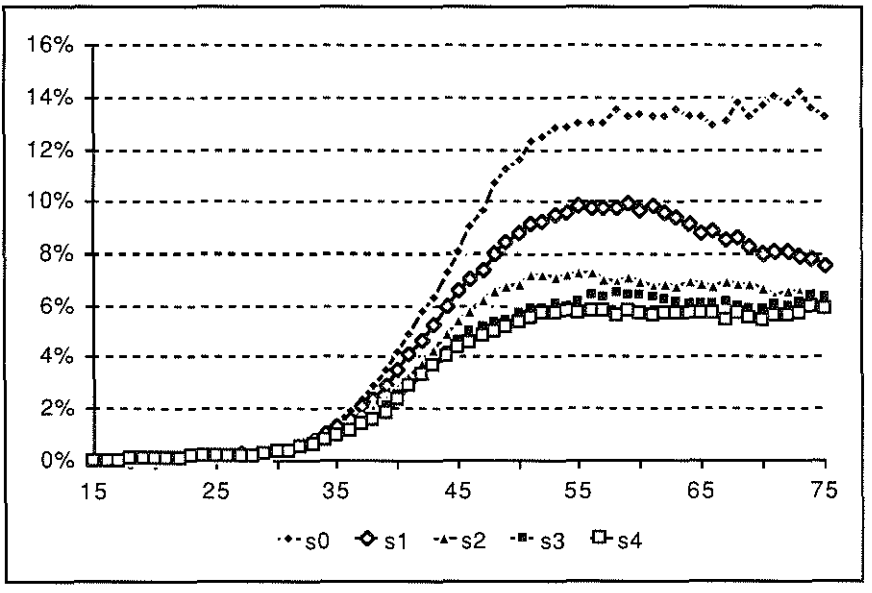

Figure 11.8 - Relative prevalence of blindness for males by age (years); option α

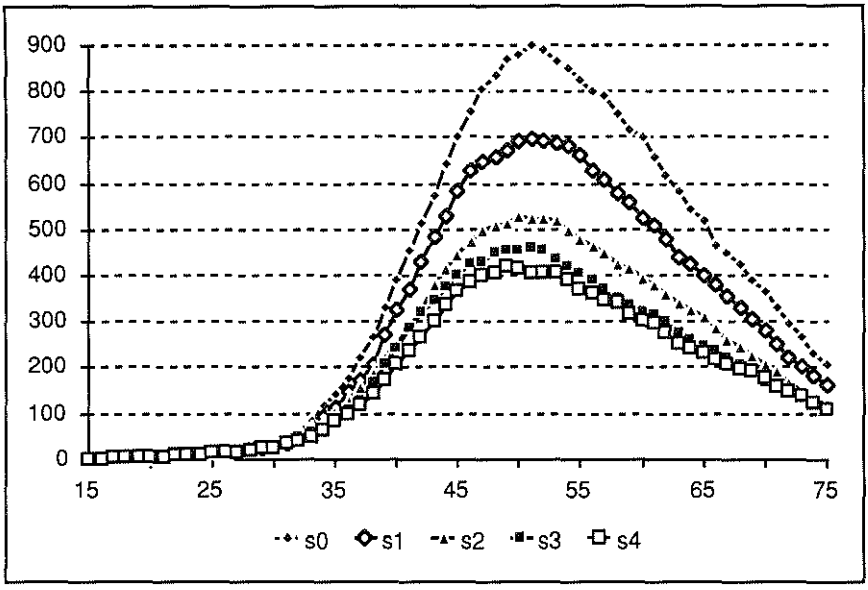

Figure 11.9 - Absolute prevalence of blindness for females by age (years); option α

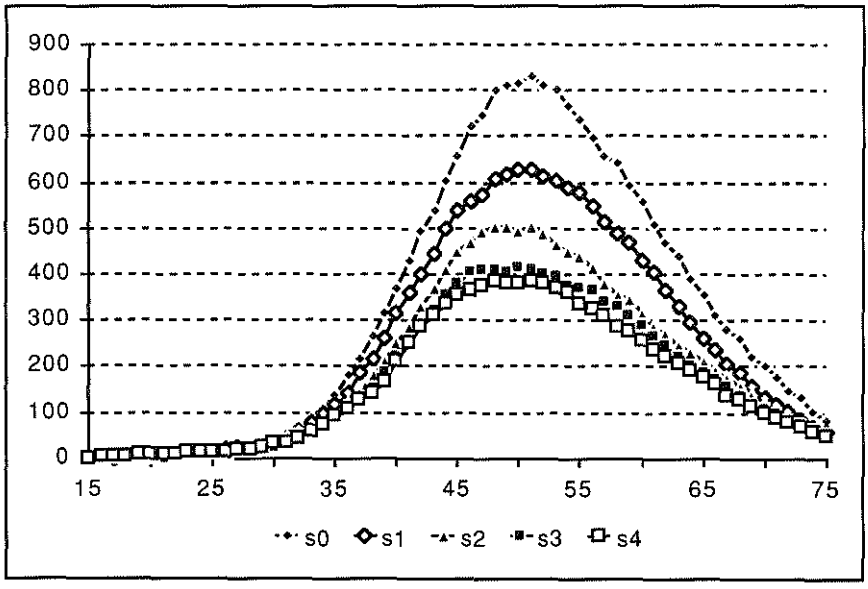

Figure 11.10 - Absolute prevalence of blindness for males by age (years); option α

The figures 11.7 to 11.10 sketch the simulation results which constitute the basis of table 11.2. If ophthalmic care is absent, the maximum prevalence rate of blindness fluctuates near 13%. In s3 and s4, the prevalence rate decreases to 6%, approximately. For men and women, the absolute prevalence of blindness reaches its maximum near the age of 50 years. This endorses the following statement in the third paragraph of the first chapter. *"Blindness among diabetic patients therefore concentrates on economically active age groups which usually contribute most extensively to production."* Figure 11.9 and figure 11.10 indicate that ophthalmic care concentrates the reduction of blindness on the same age groups.

	Females		Males	
s0	79031	100.00%	67520	100.00%
s1	68527	86.71%	59984	88.84%
s2	66168	83.72%	57131	84.61%
s3	63954	80.92%	56045	83.01%
s4	63941	80.91%	54943	81.37%

Table 11.3 - Cumulative prevalence of visual impairment (years and % of s0); option α

Table 11.3 summarises the results concerning the prevalence of visual impairment. Besides blindness, ophthalmic care reduces visual impairment. However, it is relatively less effective in combating visual impairment, as the cumulative prevalence drops by 19.09% maximally (females, s0 → s4).

In retrospect, the absolute prevalence of blindness seems to offer more valuable information than the relative prevalence. Hence, this section contains no graphs on the relative prevalence of visual impairment. According to figure 11.11 and figure 11.12, the absolute prevalence of visual impairment reaches maxima at ages ranging from 45 to 50 years. Ophthalmic care reduces visual impairment principally between the age of 45 and 65 years. Consequently, the economically active age groups are again the leading beneficiaries of ophthalmic care.

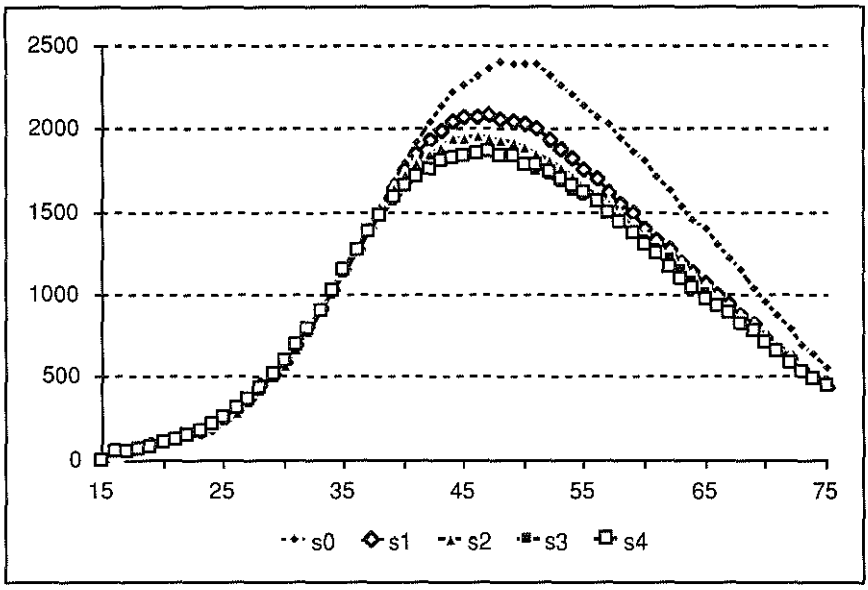

Figure 11.11 - Absolute prevalence of visual impairment for females by age (years); option α

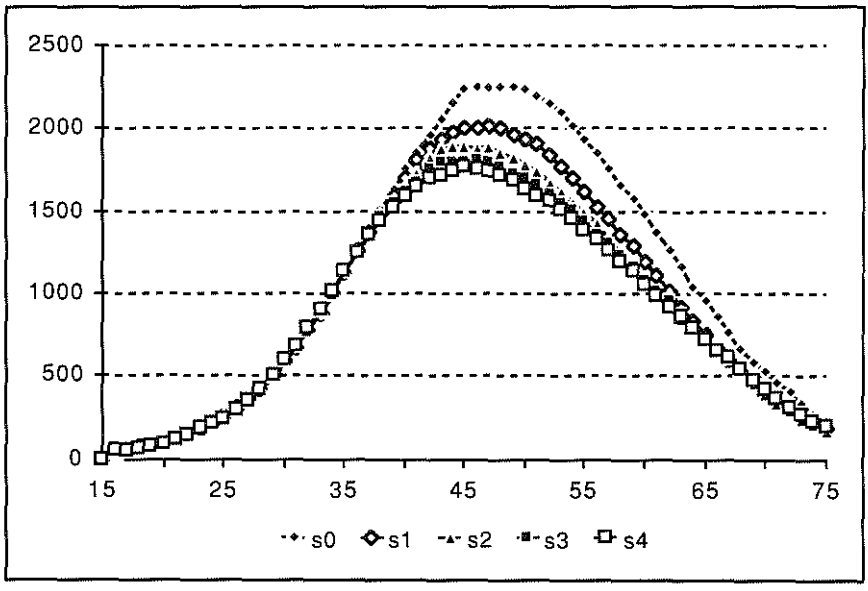

Figure 11.12 - Absolute prevalence of visual impairment for males by age (years); option α

11.4 Ophthalmoscopy, Fluorescein Angiography, and Photocoagulation

This section, like subsequent sections, cumulates the results of female and male patients in order to economise space. Figure 11.13 presents the total number of ophthalmic examinations by age in four scenarios. The curves for s1, s2, and s3 reveal zigzag patterns, because diabetic patients without DR undergo one ophthalmic examination once every eight, four, or two years, respectively. As patients grow older, the zigzag fluctuations weaken in s1, after they have deadened in s3 followed by s2. This is caused by increasing prevalence rates of DR, ME, and PDR that induce higher screening frequencies.

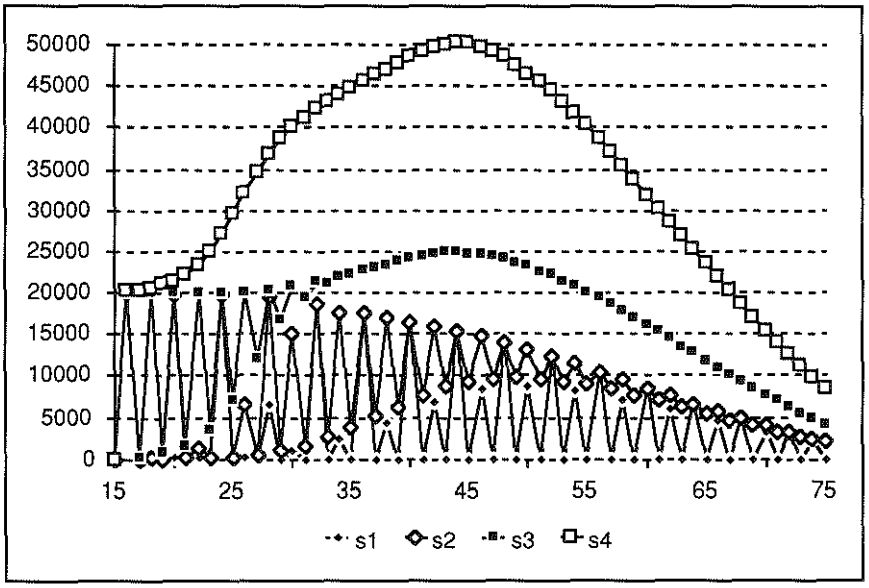

Figure 11.13 - Number of ophthalmic examinations by age (years); option α

Age	s1	s2	s3	s4	s2 / s1	s3 / s1	s4 / s1
25	40114	61990	113172	231353	155%	282%	577%
35	69331	149205	309181	629474	215%	446%	908%
45	130980	268596	549808	1114871	205%	420%	851%
55	183573	381455	777116	1572144	208%	423%	856%
65	222899	458917	933829	1884145	206%	419%	845%
75	240984	495953	1008561	2033117	206%	419%	844%
109	246128	505740	1028064	2071798	205%	418%	842%

Table 11.4 - Cumulative number of ophthalmic examinations; option α

Table 11.4 presents the number of ophthalmic examinations for female plus male patients cumulated from the start of the simulation. The comparison of the four scenarios reveals that this cumulative number increases approximately commensurate with the intensity of ophthalmic care. The last three columns indicate, that scenario two, three, and four demand approximately two, four, and eight times the cumulative number of ophthalmic examinations in scenario one.

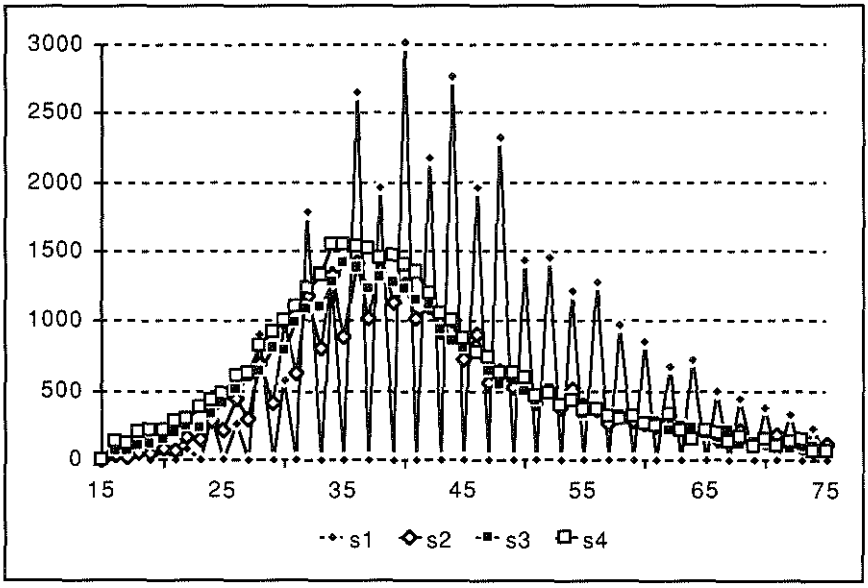

Figure 11.14 - Number of fluorescein angiograms by age (years); option α

Figure 11.14 illustrates the total number of fluorescein angiograms (FA) for female plus male patients by age, in option α (cf. table 8.5 in section 8.8). Scenario one deviates clearly from the other three scenarios: (1) the number of FAs shows a zigzag movement, which is completely, or almost completely, absent in other scenarios; (2) the maximum number of FAs is nearly twice as high; (3) that maximum is reached a few years later.

age	s1	s2	s3	s4	s2 / s1	s3 / s1	s4 / s1
25	514	1095	1882	2703	213%	366%	526%
35	5323	8773	11124	13436	165%	209%	252%
45	17890	19831	22455	26309	111%	126%	147%
55	26278	25155	27636	31783	96%	105%	121%
65	30774	27762	30367	34459	90%	99%	112%
75	32644	29152	31537	35658	89%	97%	109%
109	33244	29591	32006	36384	89%	96%	109%

Table 11.5 - Cumulative number of fluorescein angiograms; option α

According to table 11.5, the growth in the number of FAs is initially more of less proportional to the intensity of ophthalmic care. This relationship changes at older ages. Ultimately, the cumulative numbers of FAs are unrelated to the intensity of ophthalmic care, as they are much the same in different scenarios. This phenomenon may be explained as follows. Chapter three indicated, that modern ophthalmic care can hardly prevent the onset of ME and PDR, although photocoagulation may slow down or stop their progression[1]. Consequently, the prevalence rates of ME and PDR are nearly equal in all scenarios, including scenario zero, and ophthalmologists will ultimately diagnose approximately the same number of severe retinal disorders in scenario one, two, three and four. Patients must therefore undergo roughly the same number of FAs in all scenarios with ophthalmic care. Because of the longer time interval between eye examinations in scenario one, ME and PDR will be diagnosed at higher ages, on average. This explains, why the curve for scenario one in figure 11.14 reaches its maximum later than the curves for scenario two, three, and four. Following catching-up effects, this maximum is also considerably higher.

1 According to section 3.3, ME and PDR have operational definitions in the simulation model. The onset of these disorders coincides with the first occurrence of a retinal condition that justifies focal/grid or panretinal photocoagulation respectively. At that time, the beneficial effects of photocoagulation may outweigh the risks. For that reason, the definitions of ME and PDR may differ from clinical classifications. This study assumes, that these differences are at present negligible.

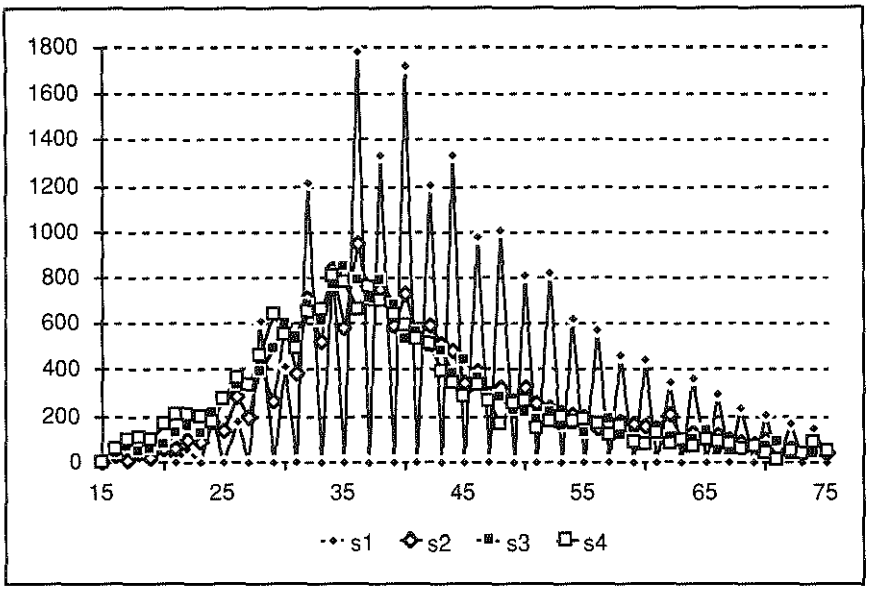

Figure 11.15 - Number of fluorescein angiograms by age (years);option β

age	s1	s2	s3	s4	s2 / s1	s3 / s1	s4 / s1
25	346	699	1188	1578	202%	343%	456%
35	3604	5484	6790	7324	152%	188%	203%
45	10994	11687	12644	12750	106%	115%	116%
55	15233	14406	14850	14924	95%	97%	98%
65	17417	15922	16060	15990	91%	92%	92%
75	18471	16642	16600	16550	90%	90%	90%
109	18815	16965	16894	16686	90%	90%	89%

Table 11.6 - Cumulative number of fluorescein angiograms; option β

According to figure 11.15 and table 11.6, option β presents an analogous picture, although the maxima are considerably lower than in option α. Surprisingly enough, the cumulative numbers of FAs are smaller in scenario two, three, and four than in scenario one. This is caused by the lengthier time interval between eye examinations in scenario one. Consequently, ME and PDR may remain unnoticed for a longer period, while causing serious retinal damage, that inhibits the effectiveness of laser treatment. A fixed fraction of these patients will have a FA for diagnostic reasons. As the model does not exclude regression, the fraction of patients receiving a FA relates always to all patients who may receive laser treatment. However, patients who received laser treatment some years earlier, are not included in this calculation. This explains why the number of FAs is smaller in scenario two, three, and four than in scenario one.

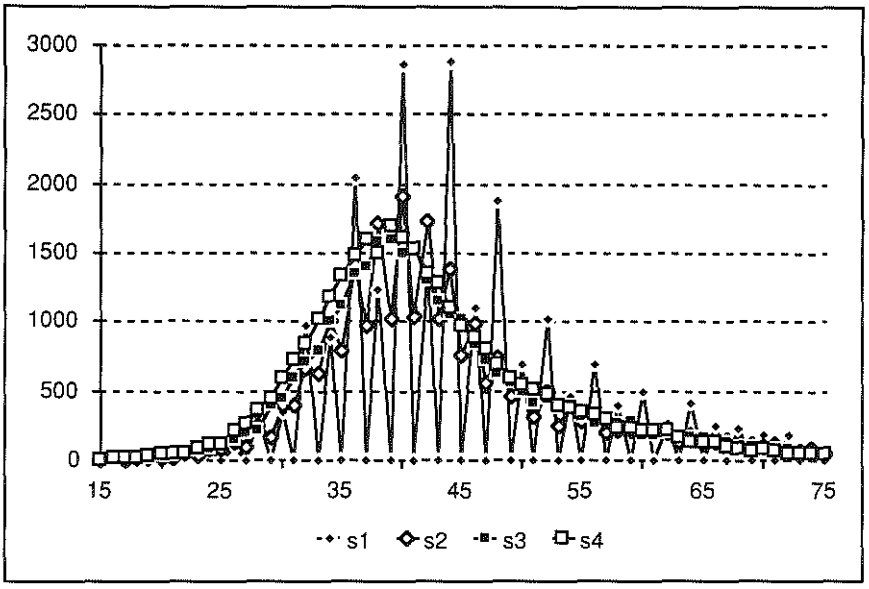

Figure 11.16 - Number of panretinal laser treatments by age (years); option α

age	s1	s2	s3	s4	s2 / s1	s3 / s1	s4 / s1
25	125	270	414	527	216%	331%	422%
35	2737	4764	6038	7482	174%	221%	273%
45	13128	17732	19541	21606	135%	149%	165%
55	18282	22727	24702	27254	124%	135%	149%
65	20532	24640	26870	29392	120%	131%	143%
75	21445	25621	27716	30086	119%	129%	140%
109	21758	25885	27914	30241	119%	128%	139%

Table 11.7 - Cumulative number of panretinal laser treatments; option α

According to figure 11.16 and table 11.7, the number of panretinal laser treatments follows the number of FAs in option α, rather closely. In scenario one, the maximum annual number of laser treatments is nearly twice as high as in scenario three and four. The cumulative number of laser treatments is 39% larger in scenario four as compared to scenario one. Consequently, the increase in the number of laser treatments is disproportionate to the rise in the intensity of ophthalmic care, measured by the frequency of ophthalmic examinations. Laser treatments are performed a few years earlier in scenarios with more intensive ophthalmic care: in scenario one on average at the age of 45.04 years ($\sigma = 10.43$) and in scenario four on average at the age of 42.00 years ($\sigma = 9.82$) (t-test: $p < 0.001$). Apparently, this time difference contributes to a considerably higher effectiveness of laser treatments.

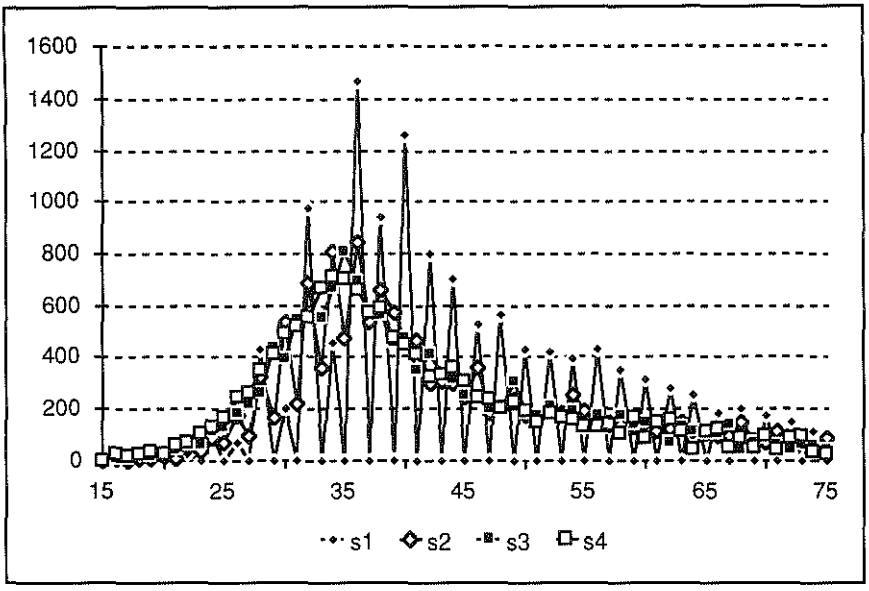

Figure11.17 - Number of focal plus grid laser treatments by age (years); option α

age	s1	s2	s3	s4	s2 / s1	s3 / s1	s4 / s1
25	146	292	484	657	200%	332%	450%
35	2277	4119	5108	5573	181%	224%	245%
45	7446	8803	9547	10051	118%	128%	135%
55	9779	10974	11530	11932	112%	118%	122%
65	11405	12285	12842	13133	108%	113%	115%
75	12229	13149	13548	13812	108%	111%	113%
109	12517	13397	13780	14040	107%	110%	112%

Table 11.8 - Cumulative number of focal plus grid laser treatments; option α

Figure 11.17 shows, that the number of focal plus grid laser treatments progresses similarly to the number of panretinal laser treatments. The order of magnitude is different, however. Besides one focal or grid treatment, there are two panretinal treatments. Furthermore, the maxima are reached somewhat earlier, because ME develops at a slightly younger age on a larger scale, in comparison to PDR (cf. figure 11.3 and figure 11.4). According to table 11.8, the cumulative number of focal plus grid laser treatments is approximately the same in all scenarios offering ophthalmic care. This is quite surprising, because scenario four counts 8.42 times more ophthalmic examinations than scenario one (cf. table 11.4). Consequently, more intensive ophthalmic care is not so much a means to recognise a larger number of eyes in need for laser treatment, because ultimately most of these eyes would also be discovered in a series of less frequent eye examinations. A higher intensity of ophthalmic care is rather a strategy for increasing effectiveness by timelier diagnosis and treatment.

How should the total numbers in table 11.8 be attributed to focal and grid laser treatments respectively? The simulation model cannot answer that question, as ME represents both exudative DR and macular edema (cf. section 3.3). Following verbal information by expert ophthalmologists, the model presumes both treatments being given in the same frequency. In other words, half these laser treatments are focal, the other half grid.

11.5 Direct Costs

Table 11.9 presents present values of the cumulative direct costs for female and male patients in option α, at three discount rates. Present values are expressed in Dutch guilders (*f*) and relate to the start of the simulation. As the simulation follows the patients on average some 44 years, positive discount rates affect the results considerably. It is not surprising, that this effect is more obvious regarding the entries *Fluorescein Angiography* and *Photocoagulation* than *Ophthalmoscopy*. Patients have eye examinations from the start of the simulation. Not until later, they receive laser treatments, after the onset of ME and PDR.

From scenario one to scenario two, as well as from scenario two to scenario three, the entry *Ophthalmoscopy* doubles its value approximately, because eye examinations become twice as frequent. However, from scenario three to scenario four the costs of eye examinations increase by far less than 100%. This is due to the actual structure of ophthalmic care charges in the Netherlands (cf. table 9.2, section 9.6) and constitutes a peculiar consequence of using care charges rather than cost prices. Dutch sickness funds, financing the social health insurance system, refund one eye examination per patient per year. Ophthalmologists receive no reimbursement for subsequent eye examinations in the same year. Patients with BR have two eye examinations per year, in scenario four (cf. table 8.1, section 8.4). These patients are quite numerous, as most years reveal a considerable gap between the prevalence of DR, ME, and PDR (cf. figure 11.4 to figure 11.6, section 11.3). In the light of the results previously presented by the tables 11.5, 11.7, and 11.8, it is hardly surprising, that the costs of fluorescein angiograms and laser treatments rise moderately from scenario one to scenario four.

		Annual discount rate		
		0%	5%	10%
s1	Ophthalmoscopy	ƒ 11,795,684	ƒ 3,630,238	ƒ 1,819,234
	Fluorescein angiography	ƒ 10,275,720	ƒ 2,517,477	ƒ 821,086
	Focal / grid photocoagulation	ƒ 18,457,881	ƒ 4,709,294	ƒ 1,580,235
	Panretinal photocoagulation	ƒ 40,230,542	ƒ 9,887,446	ƒ 3,046,359
	Total	ƒ 80,759,828	ƒ 20,744,455	ƒ 7,266,914
s2	Ophthalmoscopy	ƒ 24,237,590	ƒ 7,157,503	ƒ 3,335,574
	Fluorescein angiography	ƒ 9,146,578	ƒ 2,624,763	ƒ 986,383
	Focal / grid photocoagulation	ƒ 19,755,551	ƒ 5,547,255	ƒ 2,034,725
	Panretinal photocoagulation	ƒ 47,861,365	ƒ 12,636,514	ƒ 4,121,700
	Total	ƒ 101,001,084	ƒ 27,966,035	ƒ 10,478,382
s3	Ophthalmoscopy	ƒ 49,269,967	ƒ 14,328,075	ƒ 6,459,504
	Fluorescein angiography	ƒ 9,893,055	ƒ 3,021,780	ƒ 1,211,121
	Focal / grid photocoagulation	ƒ 20,320,333	ƒ 6,056,355	ƒ 2,338,993
	Panretinal photocoagulation	ƒ 51,612,986	ƒ 14,088,358	ƒ 4,758,935
	Total	ƒ 131,096,340	ƒ 37,494,568	ƒ 14,768,553
s4	Ophthalmoscopy	ƒ 61,428,811	ƒ 17,847,258	ƒ 7,957,324
	Fluorescein angiography	ƒ 11,246,294	ƒ 3,561,150	ƒ 1,486,604
	Focal / grid photocoagulation	ƒ 20,703,735	ƒ 6,415,057	ƒ 2,574,100
	Panretinal photocoagulation	ƒ 55,915,609	ƒ 15,775,296	ƒ 5,495,685
	Total	ƒ 149,294,449	ƒ 43,598,761	ƒ 17,513,713

Table 11.9 - Cumulative direct costs; option α

Comparing table 11.9 to table 11.10 reveals that option α and option β generate approximately the same level of direct costs, apart from the entry *Fluorescein angiography*. The sums in the two tables constitute the outcome of two fully separate simulations based on the same model. They therefore give rough indications on the stability of the simulation technique. The average absolute difference between two corresponding sums equals 1.1%, excluding FA. The maximum difference related to the entry *Ophthalmoscopy* is 0.7%. For *Photocoagulation*, absolute differences equal 4.4% or less. These percentages reflect model fluctuations as well as diagnosis differences between the options α and β. Higher frequencies of FAs reduce the likelihood of diagnostic errors in option α.

		Annual discount rate		
		0%	5%	10%
s1	Ophthalmoscopy	ƒ 11,838,529	ƒ 3,642,859	ƒ 1,823,278
	Fluorescein angiography	ƒ 5,815,717	ƒ 1,501,197	ƒ 511,784
	Focal / grid photocoagulation	ƒ 18,018,443	ƒ 4,649,402	ƒ 1,571,443
	Panretinal photocoagulation	ƒ 40,526,382	ƒ 10,065,021	ƒ 3,118,223
	Total	ƒ 76,199,071	ƒ 19,858,479	ƒ 7,024,728
s2	Ophthalmoscopy	ƒ 24,278,613	ƒ 7,169,658	ƒ 3,339,972
	Fluorescein angiography	ƒ 5,243,882	ƒ 1,545,795	ƒ 594,838
	Focal / grid photocoagulation	ƒ 20,102,088	ƒ 5,672,352	ƒ 2,087,325
	Panretinal photocoagulation	ƒ 48,845,033	ƒ 12,841,448	ƒ 4,184,524
	Total	ƒ 98,469,616	ƒ 27,229,252	ƒ 10,206,659
s3	Ophthalmoscopy	ƒ 49,611,337	ƒ 14,381,856	ƒ 6,474,396
	Fluorescein angiography	ƒ 5,304,156	ƒ 1,692,726	ƒ 708,176
	Focal / grid photocoagulation	ƒ 20,401,437	ƒ 6,155,697	ƒ 2,406,863
	Panretinal photocoagulation	ƒ 52,470,922	ƒ 14,394,044	ƒ 4,886,921
	Total	ƒ 127,787,852	ƒ 36,624,323	ƒ 14,476,356
s4	Ophthalmoscopy	ƒ 61,522,653	ƒ 17,878,702	ƒ 7,971,079
	Fluorescein angiography	ƒ 5,467,670	ƒ 1,838,772	ƒ 812,525
	Focal / grid photocoagulation	ƒ 20,514,983	ƒ 6,567,535	ƒ 2,693,134
	Panretinal photocoagulation	ƒ 56,718,075	ƒ 16,187,359	ƒ 5,681,650
	Total	ƒ 144,223,381	ƒ 42,472,367	ƒ 17,158,387

Table 11.10 - Cumulative direct costs; option β

11.6 Effects and Benefits

The effects of ophthalmic care may be approached from different angles. If patients are classified either in the category *blind* or *sighted*, the effects may be measured by (1) *prevented vision loss* and (2) *realised sight gain*. For the first measurement method, the discounted cumulative prevalence of blindness is determined per scenario. In other words, at each discount rate five amounts emerge corresponding to s0, s1, s2, s3, and s4 respectively. *Prevented vision loss* equals the difference of two amounts, each related to one scenario. The second method computes the discounted cumulative prevalence of non-blindness per scenario. *Realised sight gain* equals the prevalence difference of non-blindness in two scenarios.

Annual discount rate		s0	s1	s2	s3	s4
		Realised sight gain (years)				
0%	s0		26284	39815	46502	46420
	s1	9635		13531	20218	20136
	s2	17305	7670		6687	6605
	s3	20968	11333	3663		-82
	s4	22578	12942	5273	1609	
5%	s0		2975	4934	5827	5871
	s1	1509		1959	2852	2896
	s2	2750	1241		893	936
	s3	3366	1857	616		44
	s4	3635	2127	886	269	
10%	s0		450	843	1005	988
	s1	310		393	555	539
	s2	574	264		162	146
	s3	712	402	138		-17
	s4	756	446	182	44	
		Prevented vision loss (years)				

Table 11.11 - Cumulative realised sight gain and prevented vision loss; option α

Table 11.11 denotes the results by both measurement methods, rounded to integers. The three principal rectangular blocks represent three discount rates. A diagonal line divides each block into two triangles. The lower triangles represent *prevented vision loss*, whereas the upper triangles indicate *realised sight gain*. It may be useful to examine the meaning of these numbers by two examples. The first concerns the number 22,578, which is the first item on the last line of the block for discount rate 0%. This number reflects the cumulative prevalence of blindness in scenario zero, 44,629 (=24,529 + 20,100), minus the corresponding sum in scenario four, 22,051 (=11,860 + 10,191). These sums are taken from table 11.2 in section 11.3. In other words at a discount rate of 0%, the cumulative prevalence of blindness is 22,578 years larger in scenario zero than in scenario four.

$$B^{c,i} = \sum_{s = \text{female}}^{\text{male}} \sum_{t=1}^{\infty} \frac{B^{c}_{s,t}}{(1+i)^{(t-0.5)}} \qquad (11.1)$$

$$\{c \in \{0, 1, 2, 3, 4\}; i \in \mathbb{R}; s \in \{\text{female}, \text{male}\}; B, t \in \mathbb{Z}^{+}\}$$

Equation 11.1 formalises the calculation of the discounted cumulative prevalence of blindness $B^{c,i}$ in scenario c at discount rate i. The variables s and t indicate the gender

and the time expressed in years since the start of the simulation, respectively. $B^c_{s,t}$ represents the non-discounted prevalence of blindness in scenario c for gender s in year t.

The second example relates to the number 393, which is the second item on the second line of the third block in table 11.11 (discount rate: 10%). This number equals the discounted realised sight gain after intensifying ophthalmic care from scenario one to scenario two. For both scenarios, the prevalence of non-blindness is determined by an equation, that is essentially identical with equation 11.1. From simulation results not presented in this manuscript, this formula leads to 190,709 years non-blindness in scenario two and to 190,316 years in scenario one, at an annual discount rate of 10%. This implies, that all patients together can see 393 years longer in scenario two as compared to scenario one. In brief, table 11.11 may be read in two ways. Regarding *Realised sight gain*, the line indicates the scenario before intensifying ophthalmic care, whereas the column mentions the scenario after care intensification. The opposite is valid for *Prevented vision loss*.

According to table 11.11, *Realised sight gain* usually surpasses *Prevented vision loss*. These differences relate to increases in life expectation that accompany ophthalmic care (cf. table 11.1, section 11.2). Consequently, DR can threaten the retina for a longer period, which may increase the cumulative prevalence of blindness. As a result, *Prevented vision loss* confuses effects of laser treatments and changes in life expectation. These two factors alter the prevalence of blindness in opposite directions. Therefore, *Prevented vision loss* underestimates the effects of ophthalmic care. *Realised sight gain* enables avoiding this pitfall. However, this measure does not distinguish the pure effect of laser treatments and the consequences of increases in life expectation, presented in table 11.1.

It is quite justifiable to ask why this analysis refers to both measures. Principally, physicians aim at optimising the healthiness and the length of each patient's life. Following these strivings, *Realised sight gain* indicates qualitative as well as quantitative contributions to the life of diabetic patients by ophthalmic care. This pleads for preferring this measure to *Prevented vision loss*. For the sake of completeness, the economic assessment in this investigation uses both measures to evaluate the consequences of the central issue in this study.

All numbers in the lower triangles of the three main blocks in figure 11.11 are positive. Hence in all cases, intensifying ophthalmic care results in reductions of vision loss. Most numbers concerning *Realised sight gain* are positive, except for the transition from scenario three to scenario four, at a discount rate of 0% and 10%. As table 11.1

in section 11.2 indicates, this transition manifests a slight reduction in the life expectation of both female and male patients. This phenomenon hinders eye care in increasing the prevalence of non-blindness. It may be surprising, that the corresponding outcome at a discount rate of 5% is positive: +44. This is purely the result of a quite peculiar spread in time of the prevalence of non-blindness. Prior to the discussion in the next chapter, it may be worthwhile to notice that scenario four is hardly more effective than scenario three in combating blindness.

According to table 11.11 and 11.12, the *Realised sight gain* is sometimes over twice as large as the *Prevented vision loss*. This substantial difference is related to the nature of these measures. In both tables, each number equals the difference of two numbers, which represent the difference of two other numbers. Such balance variables have the following peculiar characteristic. The balance of two numbers may become less stable, if that balance becomes smaller in comparison to the two numbers. The second example, illustrating figure 11.11, where 393 was the balance of 190,709 and 190,316, may clarify this. A minor change in the two latter numbers may result in a comparatively large change of their balance. This explains, why a rather insignificant increase in the life expectation, indicated in table 11.1, may cause substantial deviations between the two standards to measure the visual effects of ophthalmic care.

Annual discount rate		s0	s1	s2	s3	s4
		Realised sight gain (years)				
0%	s0		27397	39572	48131	44751
	s1	10768		12175	20735	17354
	s2	17454	6686		8559	5179
	s3	21108	10341	3654		-3380
	s4	22605	11838	5151	1497	
5%	s0		3338	5195	6252	5689
	s1	1582		1857	2914	2351
	s2	2702	1120		1057	494
	s3	3406	1824	704		-563
	s4	3650	2067	947	243	
10%	s0		556	978	1186	988
	s1	311		422	630	432
	s2	536	225		208	10
	s3	728	418	193		-198
	s4	779	468	243	50	
		Prevented vision loss (years)				

Table 11.12 - Cumulative realised sight gain and prevented vision loss; option β

Table 11.12 presents the results of option β. The differences with table 11.11 have a tangled pattern. In some cases, option α presents more favourable results, in other cases option β. According to table 11.12, the *Realised sight gain* from scenario three to scenario four is always negative. Again, this may be due to the slight reduction in the life expectation for all patients from scenario three to scenario four.

		Annual discount rate		
		0%	5%	10%
s1	Production growth	ƒ 1,012,345,500	ƒ 154,023,574	ƒ 30,703,865
	Disability facilities savings	ƒ 92,307,726	ƒ 14,342,239	ƒ 2,954,926
	Total	ƒ 1,104,653,226	ƒ 168,365,813	ƒ 33,658,791
s2	Production growth	ƒ 1,508,371,500	ƒ 240,857,672	ƒ 50,616,258
	Disability facilities savings	ƒ 154,745,317	ƒ 24,759,848	ƒ 5,265,217
	Total	ƒ 1,663,116,817	ƒ 265,617,520	ƒ 55,881,475
s3	Production growth	ƒ 1,734,292,500	ƒ 284,452,596	ƒ 60,759,396
	Disability facilities savings	ƒ 185,369,122	ƒ 30,067,765	ƒ 6,479,647
	Total	ƒ 1,919,661,622	ƒ 314,520,361	ƒ 67,239,043
s4	Production growth	ƒ 1,796,100,000	ƒ 293,288,605	ƒ 61,835,397
	Disability facilities savings	ƒ 194,925,959	ƒ 31,680,079	ƒ 6,736,096
	Total	ƒ 1,991,025,959	ƒ 324,968,684	ƒ 68,571,493

Table 11.13 - Cumulative indirect and direct benefits; option α

The simulation distinguishes indirect benefits, generated by savings on production losses (= production growth), and direct benefits from savings on disability facilities. As before, all amounts are expressed in Dutch guilders (*ƒ*). Patients are classified annually into ten categories of visual acuity (VA) in their better eye: (1) $0.0 \leq VA \leq 0.1$; (2) $0.1 < VA \leq 0.2$; ... (10) $0.9 < VA \leq 1.0$. Table 11.13 is based on this classification and employs scenario zero as basis. The results signal diminishing marginal returns of ophthalmic care, like the earlier results in table 11.2 and table 11.3 (section 11.3). Most benefits are indirect, because they originate from savings in production losses. However, some scepticism seems appropriate, because these amounts are based on the *human capital approach*. The *friction costs method* might reduce these savings to roughly one tenth [Koopmanschap 92].

Table 11.14 presents the benefits in option β. At a discount rate of 0% in scenario one, option β offers larger total benefits than option α. However, the opposite is true in all other situations.

		Annual discount rate		
		0%	5%	10%
s1	Production growth	ƒ 1,055,063,250	ƒ 149,926,028	ƒ 27,641,446
	Disability facilities savings	ƒ 100,572,885	ƒ 14,710,915	ƒ 2,882,380
	Total	ƒ 1,155,636,135	ƒ 164,636,942	ƒ 30,523,826
s2	Production growth	ƒ 1,485,331,500	ƒ 228,146,758	ƒ 44,292,532
	Disability facilities savings	ƒ 153,977,390	ƒ 23,950,587	ƒ 4,820,744
	Total	ƒ 1,639,308,890	ƒ 252,097,345	ƒ 49,113,276
s3	Production growth	ƒ 1,670,931,750	ƒ 270,826,844	ƒ 56,101,437
	Disability facilities savings	ƒ 182,807,325	ƒ 29,509,796	ƒ 6,288,059
	Total	ƒ 1,853,739,075	ƒ 300,336,640	ƒ 62,389,496
s4	Production growth	ƒ 1,787,876,250	ƒ 284,433,647	ƒ 57,956,635
	Disability facilities savings	ƒ 195,038,651	ƒ 31,307,678	ƒ 6,655,494
	Total	ƒ 1,982,914,901	ƒ 315,741,325	ƒ 64,612,129

Table 11.14 - Cumulative indirect and direct benefits; option β

11.7 Average and Marginal Analysis

The upper block of table 11.15 presents ratios of direct costs (cf. table 11.9) and realised sight gain (cf. table 11.11) for option α. The lower block relates direct costs to prevented vision loss by taking statistics from the same tables. In each block, the first four lines reflect average results, whereas the last three lines indicate marginal results, following the distinction presented with some hesitation in section 9.3. Scenario zero, without ophthalmic care, is the basis for average results, whereas the marginal analysis compares two *"neighbouring"* scenarios. Consequently, the comparison of scenario zero with scenario one belongs to the average and the marginal analysis.

The amounts in the upper block are smaller than in the lower block, except for two marginal results from scenario three to scenario four. This is not surprising, because realised sight gain usually exceeds prevented vision loss (cf. table 11.11). In both blocks, scenario two yields the lowest average costs per year realised sight gain or prevented vision loss. In the upper block, the smallest average amount equals 78% of the largest average amount. The corresponding percentage equals 70% in the lower block. Because the marginal costs from scenario one to scenario two are smaller than the average costs in scenario one, the average costs are smaller in scenario two than in scenario one, according to the principles of marginal analysis. The marginal costs increase, when ophthalmic care intensifies from scenario one onwards. The two negative amounts on the last line of the upper block result from the two negative sums in table

11.11, which reflect a reduction in realised sight gain. Higher discount rates lead to increases in average and marginal costs, except for the negative amounts. This implies that the centre of gravity of the direct costs is situated earlier in time than the centre of gravity of realised sight gain and prevented vision loss.

		Annual discount rate		
		0%	5%	10%
Direct costs / Realised sight gain	s0 -> s1	f 3,073	f 6,973	f 16,159
	s0 -> s2	f 2,537	f 5,668	f 12,433
	s0 -> s3	f 2,819	f 6,435	f 14,692
	s0 -> s4	f 3,216	f 7,426	f 17,719
	s1 -> s2	f 1,496	f 3,686	f 8,170
	s2 -> s3	f 4,501	f 10,676	f 26,421
	s3 -> s4	-f 222,607	f 138,908	-f 163,822
Direct costs / Prevented vision loss	s0 -> s1	f 8,382	f 13,752	f 23,441
	s0 -> s2	f 5,837	f 10,171	f 18,255
	s0 -> s3	f 6,252	f 11,139	f 20,736
	s0 -> s4	f 6,613	f 11,993	f 23,164
	s1 -> s2	f 2,639	f 5,819	f 12,165
	s2 -> s3	f 8,215	f 15,457	f 31,037
	s3 -> s4	f 11,308	f 22,656	f 62,595

Table 11.15 - Direct costs related to realised sight gain and prevented vision loss; option α

		Annual discount rate		
		0%	5%	10%
Direct costs / Realised sight gain	s0 -> s1	f 2,781	f 5,949	f 12,635
	s0 -> s2	f 2,488	f 5,242	f 10,441
	s0 -> s3	f 2,655	f 5,858	f 12,206
	s0 -> s4	f 3,223	f 7,465	f 17,374
	s1 -> s2	f 1,829	f 3,969	f 7,548
	s2 -> s3	f 3,425	f 8,889	f 20,481
	s3 -> s4	-f 4,862	-f 10,394	-f 13,515
Direct costs / Prevented vision loss	s0 -> s1	f 7,077	f 12,551	f 22,597
	s0 -> s2	f 5,642	f 10,077	f 19,047
	s0 -> s3	f 6,054	f 10,752	f 19,873
	s0 -> s4	f 6,380	f 11,638	f 22,030
	s1 -> s2	f 3,331	f 6,582	f 14,141
	s2 -> s3	f 8,023	f 13,341	f 22,175
	s3 -> s4	f 10,979	f 24,040	f 53,190

Table 11.16 - Direct costs related to realised sight gain and prevented vision loss; option β

Table 11.16 is based on the costs in table 11.10 and the realised sight gain or prevented vision loss in table 11.12. Otherwise, this table is essentially the same as table 11.15. Virtually all the average results in table 11.16 are smaller than the corresponding results in table 11.15. The marginal results do not reveal a coherent pattern.

The tables 11.17 to 11.20 conclude the economic evaluation by confronting costs and benefits with realised sight gain and prevented vision loss. The quotients 11.2 are the formal equivalents of the results in these tables. The symbols $C^{0\rightarrow c,i}$ indicate the mutation in the total direct costs from scenario zero to scenario c discounted at rate i. The symbols regarding benefits, $F^{0\rightarrow c,i}$ and $Q^{0\rightarrow c,i}$, relate respectively to savings in disability facilities and production losses. Finally, the symbols $V^{0\rightarrow c,i}$ indicate realised sight gain or prevented vision loss. Analogously, $C^{(c-1)\rightarrow c,i}$, $F^{(c-1)\rightarrow c,i}$, $Q^{(c-1)\rightarrow c,i}$, and $V^{(c-1)\rightarrow c,i}$ represent money values or numbers related to the intensification of ophthalmic care from scenario c–1 to scenario c.

$$\text{Average analysis} \quad \frac{C^{0\rightarrow c,i} - F^{0\rightarrow c,i} - Q^{0\rightarrow c,i}}{V^{0\rightarrow c,i}}$$

$$\text{Marginal analysis} \quad \frac{C^{(c-1)\rightarrow c,i} - F^{(c-1)\rightarrow c,i} - Q^{(c-1)\rightarrow c,i}}{V^{(c-1)\rightarrow c,i}} \qquad (11.2)$$

$$\{c \in \{1, 2, 3, 4\}; i \in \mathbf{R}\}$$

In both quotients, the numerator as well as the denominator may be positive or negative. This provokes ambiguity. Negative values of the quotients, for instance, may reflect two totally opposed experiences. In the first, patients enjoy better sight, while benefits exceed costs. This is advantageous for medical and financial reasons. In the second experience, ophthalmic care has adverse effects and costs overshadow benefits. This is definitely undesirable. Positive values of the quotients 11.2 are ambiguous for similar reasons. To avoid confusion, the presentation of results is confined to positive outcomes of ophthalmic care. In other words, all the amounts disclosed by the tables 11.17 to 11.20 are based on quotients with a positive denominator. Vacant positions reflect events that should be avoided for medical reasons. Amounts are positive, if costs exceed benefits. Negative amounts reflect experiences, where medical and financial arguments plead for intensifying ophthalmic care. The total direct costs C are taken from table 11.9 or table 11.10, the total direct and indirect benefits F and Q from table 11.13 or table 11.14, and the realised sight gain of prevented vision loss V from table 11.11 or table 11.12.

$$C^{(c-1) \rightarrow c, i} = C^{0 \rightarrow c, i} - C^{0 \rightarrow (c-1), i} \qquad (11.3)$$

The tables 11.9, 11.10, 11.13, and 11.14 present average amounts. Equation 11.3 enables deriving marginal costs from average costs. Benefits are determined analogously.

		Annual discount rate		
		0%	5%	10%
Direct costs -/- Benefits / Realised sight gain	s0 -> s1	-*f* 38,955	-*f* 49,619	-*f* 58,686
	s0 -> s2	-*f* 39,235	-*f* 48,163	-*f* 53,871
	s0 -> s3	-*f* 38,463	-*f* 47,543	-*f* 52,200
	s0 -> s4	-*f* 39,676	-*f* 47,927	-*f* 51,656
	s1 -> s2	-*f* 39,778	-*f* 45,952	-*f* 48,363
	s2 -> s3	-*f* 33,865	-*f* 44,116	-*f* 43,524
	s3 -> s4	—	-*f* 98,856	—
Direct costs -/- Benefits / Prevented vision loss	s0 -> s1	-*f* 106,265	-*f* 97,859	-*f* 85,133
	s0 -> s2	-*f* 90,270	-*f* 86,433	-*f* 79,099
	s0 -> s3	-*f* 85,299	-*f* 82,302	-*f* 73,670
	s0 -> s4	-*f* 81,574	-*f* 77,397	-*f* 67,529
	s1 -> s2	-*f* 70,175	-*f* 72,545	-*f* 72,013
	s2 -> s3	-*f* 61,817	-*f* 63,873	-*f* 51,128
	s3 -> s4	-*f* 33,038	-*f* 16,123	*f* 32,212

Table 11.17 - Direct costs, benefits, realised sight gain, and prevented vision loss; option α

All the average results in table 11.17 are negative. In other words, savings in disability facilities and production losses surpass direct costs. Ophthalmic care generates positive macro-economic returns. All the marginal amounts are negative, up to scenario three. However, the transition from scenario three to scenario four has inconsistent consequences. Positive discount rates generate comparatively smaller mutations in table 11.17 than in the previous tables that supply *"raw"* statistics to determine the above results. Apparently, the mutations in these raw statistics have counterbalancing effects. In the upper block, higher discount rates generally lead to higher amounts. In the lower block, most changes have the opposite direction. As the numerators of the quotients 11.2 are equal in both blocks, only the denominators may explain these differences. The results reveal, that higher discount rates increase the weight of *Prevented vision loss*, as compared to *Realised sight gain*. Consequently, *Prevented vision loss* is concentrated in earlier years than *Realised sight gain*. This is due to the fact, that the second measure, as opposed to the first, reflects increases in life expectation. Table 11.18 presents broadly the same pattern as table 11.17.

		Annual discount rate		
		0%	5%	10%
Direct costs -/- Benefits	s0 -> s1	-ƒ 39,401	-ƒ 43,374	-ƒ 42,265
	s0 -> s2	-ƒ 38,938	-ƒ 43,286	-ƒ 39,799
	s0 -> s3	-ƒ 35,859	-ƒ 42,182	-ƒ 40,397
	s0 -> s4	-ƒ 41,087	-ƒ 48,033	-ƒ 48,049
Realised sight gain	s1 -> s2	-ƒ 37,897	-ƒ 43,130	-ƒ 36,546
	s2 -> s3	-ƒ 21,627	-ƒ 36,753	-ƒ 43,203
	s3 -> s4	—	—	—
Direct costs -/- Benefits	s0 -> s1	-ƒ 100,250	-ƒ 91,500	-ƒ 75,593
	s0 -> s2	-ƒ 88,281	-ƒ 83,221	-ƒ 72,604
	s0 -> s3	-ƒ 81,768	-ƒ 77,420	-ƒ 65,776
	s0 -> s4	-ƒ 81,340	-ƒ 74,878	-ƒ 60,928
Prevented vision loss	s1 -> s2	-ƒ 69,008	-ƒ 71,522	-ƒ 68,474
	s2 -> s3	-ƒ 50,657	-ƒ 55,160	-ƒ 46,775
	s3 -> s4	-ƒ 75,311	-ƒ 39,286	ƒ 9,111

Table 11.18 - Direct costs, benefits, realised sight gain, and prevented vision loss; option β

The results presented in table 11.17 and table 11.18 may be considered somewhat sceptically in the light of the observations in section 9.5 on the *human capital approach* and the *friction costs technique*. For various reasons, estimates of production losses are likely to be more realistic by the latter method than by the former. The *friction costs technique* is still in its infancy, however. At present, there are virtually no empirical findings to determine production losses resulting from blindness by DR following this technique. In the absence of adequate empirical data, the simulation resorts to approximations based on an investigation of the cardiovascular disease [Koopmanschap 92]. In the *human capital approach*, production losses by this disorder are estimated to be over ten times as high as in the *friction costs technique*. Generally, complications due to IDDM occur at younger ages than the cardiovascular disease. The *human capital approach* may therefore lead to comparatively higher overestimates of production losses resulting from visual impairment by DR. Consequently, the savings in production losses, mentioned in table 11.13 and table 11.14, are arbitrarily divided by twenty before determining the results in table 11.19 and table 11.20. Otherwise, these results are calculated by the same method as the results in table 11.17 and table 11.18.

If the discount rate equals 0% or 5%, average benefits exceed average costs in all scenarios. At a discount rate of 10% however, average costs exceed average benefits in all scenarios. The marginal analysis confirms this trend. The results of option β, presented in table 11.20, reveal a pattern that is broadly similar to option α, although op-

tion β is slightly more auspicious, because the unweighted average of all the average results is 6.9% more favourable as compared to option α.

		Annual discount rate		
		0%	5%	10%
Direct costs -/- Benefits / Realised sight gain	s0 -> s1	-ƒ 2,365	-ƒ 437	ƒ 6,175
	s0 -> s2	-ƒ 3,244	-ƒ 1,791	ƒ 3,183
	s0 -> s3	-ƒ 3,032	-ƒ 1,166	ƒ 5,224
	s0 -> s4	-ƒ 2,918	-ƒ 468	ƒ 7,776
	s1 -> s2	-ƒ 4,952	-ƒ 3,847	-ƒ 240
	s2 -> s3	-ƒ 1,768	ƒ 2,287	ƒ 15,819
	s3 -> s4	—	ƒ 92,164	—
Direct costs -/- Benefits / Prevented vision loss	s0 -> s1	-ƒ 6,452	-ƒ 861	ƒ 8,957
	s0 -> s2	-ƒ 7,464	-ƒ 3,214	ƒ 4,673
	s0 -> s3	-ƒ 6,724	-ƒ 2,019	ƒ 7,373
	s0 -> s4	-ƒ 5,999	-ƒ 755	ƒ 10,165
	s1 -> s2	-ƒ 8,735	-ƒ 6,074	-ƒ 358
	s2 -> s3	-ƒ 3,228	ƒ 3,311	ƒ 18,582
	s3 -> s4	ƒ 3,449	ƒ 15,032	ƒ 55,520

Table 11.19 - Approximation by *friction costs technique*; option α

		Annual discount rate		
		0%	5%	10%
Direct costs -/- Benefits / Realised sight gain	s0 -> s1	-ƒ 2,815	-ƒ 704	ƒ 4,965
	s0 -> s2	-ƒ 3,279	-ƒ 1,565	ƒ 3,244
	s0 -> s3	-ƒ 2,879	-ƒ 1,028	ƒ 4,539
	s0 -> s4	-ƒ 3,133	-ƒ 537	ƒ 7,700
	s1 -> s2	-ƒ 4,324	-ƒ 3,113	ƒ 975
	s2 -> s3	-ƒ 1,027	ƒ 1,610	ƒ 190,484
	s3 -> s4	—	—	—
Direct costs -/- Benefits / Prevented vision loss	s0 -> s1	-ƒ 7,163	-ƒ 1,484	ƒ 8,879
	s0 -> s2	-ƒ 7,435	-ƒ 3,008	ƒ 5,918
	s0 -> s3	-ƒ 6,565	-ƒ 1,887	ƒ 7,390
	s0 -> s4	-ƒ 6,203	-ƒ 838	ƒ 9,764
	s1 -> s2	-ƒ 7,874	-ƒ 5,162	ƒ 1,827
	s2 -> s3	-ƒ 2,406	ƒ 2,417	ƒ 11,488
	s3 -> s4	-ƒ 1,098	ƒ 13,853	ƒ 44,064

Table 11.20 - Approximation by *friction costs technique*; option β

The next chapter presents concluding remarks on the results for IDDM patients.

12

Concluding Remarks

12.1 Introduction

According to the theory of information processing, the difference between facts and information can be rather wide. Bridging this gap may require various processes to transform empirical findings into output that suits decision making. Selections, calculations, and the rendering of results in diagrams or tables are elements of this approach. Its orientation should suit the nature of the decisions to be supported. The results, presented in the previous chapter, were obtained from the *"raw"* data of the simulation by a similar approach. For the sake of clarity, some explanatory notes accompanied most figures and tables. However, these observations were confined to separate elements of the analysis. This chapter attempts to reduce the distance between facts and information further by considering the simulation results for IDDM patients as a whole.

12.2 Epidemiologic Results

At the age of 15 years, the onset of IDDM reduces life expectation by 28% to 32% (table 11.1), which is somewhat more favourable than the reduction by one third found in empirical investigations [STG 91:30, 87]. The optimism of the simulation seems justifiable, because it concerns the near future. Due to steady advances in medical technology, IDDM patients will probably continue to benefit from a rising relative life expectation, a trend that goes back to the introduction of insulin, in the early twenties. The results reveal furthermore, that ophthalmic care benefits the life expectation marginally. This increase is not continuous, however. From scenario three to scenario four, the life expectation for female and male patients decreases by 0.085 years, or 0.19%, on average.

This may be explained as follows. The figures 11.7 to 11.12 in section 11.3 show, that the absolute and relative prevalence of blindness and visual impairment is approximately equivalent in both scenarios. Additionally, ophthalmic care affects the prevalence of blindness and moderate vision far more than the prevalence of DR, ME, and PDR. Consequently, the prevalence of DR, ME, and PDR is probably approximately the same in both scenarios, giving similar values to the factors that determine the relative life expectation. Therefore, the lower average life expectation in scenario four, in comparison to scenario three, relates primarily to the stochastic nature of this Monte Carlo simulation[1]. The differences are too small to be significant, because of the uncertainty margins of this technique.

According to the figures 11.3 to 11.6, the prevalence of DR in the simulation corresponds with the epidemiologic data by Klein and associates, which were presented in table 10.1 [84b, 89c]. The prevalence of ME adopts a middle course between the findings by Klein and co-workers, summarised in table 10.2 [84f], and the simulation by Javitt et al. [89]. For patients older than 55 years, the prevalence of ME equals on average approximately 35% in the simulation versus 26.1% among 88 patients older than 44 years in the investigation by Klein et al. This discrepancy seems justifiable for the following reasons. (1) The population size in the study by Klein et al. prohibits definite statements on the prevalence of ME among older IDDM patients. (2) For patients older than 53 years, the prevalence of ME equals 40% or more in the simulation by Javitt et al., according to a graph reading [89]. (3) ME occurs more frequently at older ages. The last observation complies with the finding, that more NIDDM patients suffer from ME than from PDR (cf. table 3.2, section 3.7). The prevalence of PDR in the simulation closely corresponds with the findings by Klein et al. [84b]. In case of discrepancies, the simulation chooses a conservative course. This may justify the statement, that the simulation imitates the actual prevalence of DR, ME, and PDR adequately.

Regarding visual impairment, the simulation also searches a compromise between the empirical findings by Klein et al. [84e], revealing a maximum prevalence of 26.7%, and the results by Javitt et al. [89], that mention a prevalence of over 50%. The compromise leans over to the epidemiologic data, as the maximum prevalence of visual impairment equals some 36%, apart from fluctuations at the end of the simulation, when

1 According to simulation results omitted in the previous chapter, the average difference in life expectation between option α and option β equals 0.03% for all scenarios. The maximum difference between two similar scenarios is 0.42%, if simulations for female and male patients are considered separately.

the number of survivors is too limited to preclude the predominance of random disturbances (cf. figure 11.3 and figure 11.4).

In this context however, the statistics on blindness are by far the most essential among all the epidemiologic results. For this very issue, the simulation chooses a conservative course to minimise the likelihood of exaggerated expectations, without loosing sight of actual findings. In the absence of ophthalmic care, the prevalence of blindness culminates at some 13% for patients older than fifty years, apart from unavoidable random fluctuations at the end of the simulation (cf. figure 11.7 and figure 11.8). This percentage approaches empirical findings by Klein and associates [84e]. According to section 10.6, other investigations would justify higher prevalence rates. Nonetheless, the simulation uses parameters that generate conservative estimates of the prevalence of blindness. Moreover, the simulation underestimates, rather than overestimates, the prevalence of blindness during the first twenty years, until the age of 35 years. Consequently, the epidemiologic results harmonise with the findings of some well-known investigations. They may therefore be considered as a solid basis for analysing the effects of ophthalmic care.

12.3 Costs, effects, and benefits

While the intensity of ophthalmic care rises, the number of ophthalmic examinations increases approximately in the same proportion (cf. table 11.4). The number of fluorescein angiograms and laser treatments, on the contrary, grows at a much lower rate, which may be even negative (cf. tables 11.5 to 11.8). Nonetheless, more intensive ophthalmic care reduces the prevalence of blindness substantially. As compared to scenario zero, where diabetic patients receive no ophthalmic care, scenario one reduces the cumulative prevalence of blindness for female and male patients on average by 21.5%, scenario two by 38.7%, scenario three by 46.9%, and scenario four by 50.5% (cf. table 11.2). Surprisingly enough, earlier versions of the simulation produced similar results and each adjustment confirmed these findings.

This outcome seems quite relevant, because the Netherlands experiences considerable shortages in ophthalmic care. To eliminate waiting lists, an extra eighty ophthalmologists in full time employment (fte) are require urgently. They would enlarge the existing corps of 385 ophthalmologists (fte) by some 20%. University schools of ophthalmology are unable to meet this demand in the short run. By the year 2005, shortages are estimated to quadruple [NOG 92:19]. In order to banish acute undersupply, additional paramedical staff members might be appointed for performing routine tasks, like

certain ophthalmic examinations, with direct supervision by ophthalmologists. The latter could then specialise in more complex tasks. By appointing extra paramedical staff members, the length of waiting lists may decrease, patients may be diagnosed earlier, laser treatments may be advanced in time, and the occurrence of complications may be postponed. This could benefit the success rates of treatments and reduce the work load of ophthalmologists in the longer run. The vicious circle that currently threatens to entangle ophthalmic care could then be broken.

The simulation expresses the effects of ophthalmic care in years of realised sight gain or prevented vision loss. Direct costs and savings in disability facilities are measured in monetary units. Both types of consequences are characterised by diminishing returns with respect to the intensity of ophthalmic care. The total benefits (cf. table 11.13 and table 11.14) equal nearly fifteen times the direct costs (cf. table 11.9 and table 11.10) at a discount rate of 0%, more than eight times at a discount rate of 5%, and four to five times at a discount rate of 10%.

		Annual discount rate		
		0%	5%	10%
Option alpha	s1	114%	69%	41%
	s2	153%	89%	50%
	s3	141%	80%	44%
	s4	131%	73%	38%
Option beta	s1	132%	74%	41%
	s2	156%	88%	47%
	s3	143%	81%	43%
	s4	135%	74%	39%

Table 12.1 - Total direct benefits as percentage of total direct costs

The percentages in table 12.1 relate to the results in the tables 11.9, 11.10, 11.13, and 11.14. According to table 12.1, the financial consequences of ophthalmic care appear interesting, even when indirect benefits are ignored. Total direct benefits exceed total direct costs by 14% to 56% at a discount rate of 0%, while they are 11% to 31% smaller at a discount rate of 5%. If the latter discount rate is the most realistic, ophthalmic care seems almost justifiable from a financial point of view, which encompasses merely a subset of all benefits.

12.4 Cost-effectiveness

Previous sections and chapters have emphasised repeatedly, that the simulation attempts to evaluate the effects and benefits of ophthalmic care along conservative lines. Regarding direct costs however, the simulation uses the uncurtailed charges of ophthalmic care which were operative in the Netherlands at the beginning of 1992[2]. From this starting point, we may now confront costs with effects and benefits. The direct costs per year realised sight gain equal *f* 5,242 to *f* 7,465 at a discount rate of 5%. (cf. table 11.15 and table 11.16). If prevented vision loss constitutes the measurement standard, direct costs vary from *f* 10,077 to *f* 13,752. At a discount rate of 5%, scenario two in option β offers the two most favourable ratios of total direct costs and vision effects, so that this scenario minimises average total costs. In comparison with scenario two, scenario three is 14% more expensive in option α and 12% more costly in option β by measuring in realised sight gain. Scenario three appears 10% more expensive in option α and 7% in option β, if effects are expressed in prevented vision loss.

Following the *human capital approach* in table 11.17 and table 11.18, the marginal analysis presents negative amounts up to scenario three in option α and option β. Consequently, the absolute balance of costs and benefits is more favourable in scenario three than in scenario one or scenario two. It is therefore legitimate on macro-economic grounds to intensify ophthalmic care up to scenario three. However, the conservative nature of this simulation scarcely tolerates the risk of overestimating benefits by the *human capital approach.* It is therefore recommendable to base decisions regarding the intensity of ophthalmic care on results by the *friction costs technique*, although this method requires using approximations. At three discount rates and in both options, scenario two offers the most favourable average cost-effectiveness ratio according to both measurement standards (cf. table 11.19 and table 11.20). Up to a discount rate of 5%, these results are negative. In other words, even a purely financial analysis justifies the institution of scenario two.

However, decisions on the intensity of ophthalmic care for diabetic patients should not only be based on these results. There are other important aspects. Research in the American state Wisconsin reveals for instance, that 48% of all IDDM patients fail to

2 Recently, ophthalmic care charges in the Netherlands were reduced by some 10% to 20%. Further reductions may follow. This improves the ratios of costs and effects as well as the balances of costs and benefits.

comply with screening intervals for ophthalmic care, although the nature of IDDM forces these patients to visit primary care physicians and hospital polyclinics frequently [Witkin 84, Dasbach 91]. If these findings also apply to the Netherlands, it may be wise to prescribe scenario three in order to realise at least scenario two for the majority of diabetic patients. Moreover, the simulation disregards all aspects of blindness and visual impairment which cannot be quantified by objective criteria. These aspects might be decisive, especially in a situation where the previous results might create hesitation, for instance between scenario two and scenario three.

Obviously, these observations do not have a prescriptive nature. The principal objective of this publication is to draw a true picture of future events which may occur in the alternatives under consideration. Non-quantifiable aspects were mentioned so as to position quantifiable results in a wider perspective.

D

Non-Insulin-Dependent Diabetes Mellitus

13

Epidemiologic Data

13.1 Introduction

Prior to the presentation of the main results for NIDDM patients in the next chapter, the following sections provide information on the epidemiologic data that constitute the base of the simulation. This survey may be considered as a further specification of table 3.2 in section 3.7. It treats DR, ME, PDR, visual impairment and blindness successively.

13.2 Diabetic Retinopathy

Table 13.1 represents key statistics taken from four epidemiologic studies on the prevalence of DR. These investigations did not reveal significant differences related to gender. However, they demonstrated unambiguously that the prevalence rates of DR depend primarily on the duration of NIDDM. The investigations by Klein and associates, regarding two different study groups, distinguished insulin taking (NIDDM-a) and not-insulin taking (NIDDM-b) patients. Paisey and co-workers published undifferentiated data, whereas Dwyer et al. identified obese and non-obese patients. The outcomes of these studies diverge considerably. This complicates the choice of simulation parameters.

The simulation fixes the prevalence ceiling for DR at the highest rates presented in table 13.1. These are borrowed from the first investigation by Klein and associates. Various arguments plead for this choice. Firstly, several other studies refer to these outcomes [e.g. Verhoeven 89:37; Dasbach 91; STG 91:45]. Secondly, the number of patients with more than 14 years of NIDDM since clinical diagnosis equalled 467 in the first study by Klein et al. versus 89 in their second investigation. Thirdly, recent publications confirm these results, for instance an article by Harris et al. [92]. It presents a

scatter diagram with two regression lines indicating the prevalence rates of NIDDM for two study populations, the first in the American state Wisconsin and the second in Western Australia. Both lines have a positive slope. Twenty years after the onset of NIDDM, the prevalence of DR exceeds 80% in the first population and approaches 60% in the second. Although the article does not provide information for later years, the empirical findings represented in the scatter diagram suggest that the upward trend in the prevalence of DR is likely to continue in subsequent years. This justifies fixing the maximum prevalence rates of DR for NIDDM-a and NIDDM-b patients at 95% and 72% respectively.

Number of years since onset of NIDDM	[Klein 84c] Wisconsin United States (N = 1370)		[Paisey 84a,b] Mexico City Mexico (N = 503)	[Dwyer 85] Rochester Minnesota USA (N = 1031)		[Klein 92a] Beaver Dam Wisconsin USA (N = 416)	
	NIDDM-a (N = 674)	NIDDM-b (N = 696)	NIDDM (N = 503)	Obese (N = 653)	Non-obese (N = 378)	NIDDM-a (N = 96)	NIDDM-b (N = 320)
≤1	—	—	—	—	—	—	20.0%
1-4	—	—	—	—	—	20.0%	23.1%
8-16	—	—	44.6%	—	—	—	—
15	84.5%	57.5%	—	—	—	—	—
20	—	—	—	30.0%	35.9%	—	—
≥20	≤ 95% §	≤ 72% §	—	—	—	80.0%	50.0%
	§ graph reading						

Table 13.1 - Prevalence rates of DR for NIDDM patients

The following results seem to justify the choice of these prevalence ceilings. According to a study of 250 NIDDM patients by Nathan and co-workers [86b], the prevalence of DR equalled 45% among some 96 patients[1] with eleven or more years of NIDDM since clinical diagnosis. Furthermore, an investigation of 1,370 patients by Klein and associates [89a] revealed that 47% of the insulin taking NIDDM patients without DR developed DR within a period of four years. For NIDDM-b patients, the corresponding percentage equalled 34.

1 This percentage was determined by graph reading. The number of patients was derived from the total number of patients (250), the average number of years since clinical diagnosis of NIDDM (8.72 years), and the adjoining standard deviation (7.78 years).

13.3 Macular Edema

Again, Klein and associates seem to offer the most valuable epidemiologic data. The statistics in table 13.2 are taken from one of their investigations [84f].

Number of years since onset of NIDDM	[Klein 84f] (N = 900) Wisconsin United States		
	NIDDM-a (N = 419)	NIDDM-a plus NIDDM-b	NIDDM-b (N = 481)
<5	—	3%	—
≥20	≤ 38% §	28%	≤ 28% §
	§ graph reading		

Table 13.2 - Prevalence rates of ME for NIDDM patients

According to this investigation, the prevalence of ME is positively correlated with a longer duration of NIDDM, a higher systolic blood pressure, insulin use, a higher glycosylated haemoglobin level and the presence of proteinuria. A diagram in this publication pictures the relationship between the duration of diagnosed NIDDM-a or NIDDM-b and the prevalence of ME. The maximum prevalence rates equal some 38% and 28% respectively. To imitate the progression of ME, the simulation uses parameters which are directly derived from these maxima. In a four-year longitudinal study by Klein and associates [89d], the incidence of ME was 8.4% among 273 NIDDM-a patients and 2.9% among 379 NIDDM-b. Initially, none of these 652 patients suffered from ME. This investigation reveals a striking difference between IDDM and NIDDM. The duration of DM is a more significant risk factor for IDDM patients than for NIDDM patients.

13.4 Proliferative Diabetic Retinopathy

Table 13.3 presents some key findings from studies by Klein and co-workers as well as by Dwyer et al.

Number of years since onset of NIDDM	[Klein 84c] (N = 1370) Wisconsin United States		[Dwyer 85] (N = 1031) Rochester Minnesota USA	
	NIDDM-a (N = 674)	NIDDM-b (N = 696)	Obese (N = 653)	Non-obese (N = 378)
≤2	—	3.0%	—	—
3-4	4.0%	—	—	—
≥15	20.1%	4.3%	—	—
20	—	—	6.3%	0.4%
≥20	≤ 32% §	≤ 15% §	—	—
	§ graph reading			

Table 13.3 - Prevalence rates of PDR for NIDDM patients

Furthermore, a cross-sectional study of 503 NIDDM patients in Mexico City by Paisey and associates revealed a prevalence rate of 8.1% [84b]. The duration of diagnosed NIDDM was significantly longer for patients with PDR than for other patients. However, the published results do not allow the establishment of a statistically significant relation between the duration of diagnosed NIDDM and the prevalence of PDR. According to an investigation of 953 Pima Indians in Arizona (United States) by Nelson and co-workers, the cumulative incidence of PDR was 14.1% after 20 years duration of NIDDM [89]. The peculiar ethnic characteristics of the study population render these results less relevant for the Netherlands. According to a four-year longitudinal investigation by Klein and associates [89a], the incidence of PDR equalled 7% among 418 NIDDM-a patients and 2% among 486 NIDDM-b patients. None of these 904 patients had PDR at the start of the study. For NIDDM-a patients, there was a significantly positive relationship between the duration of NIDDM and the likelihood of progression to PDR.

The simulation selects the empirical findings by Klein and co-workers mentioned in table 13.1 as basis for its parameters. This choice rests on considerations which are similar to those presented in the previous sections for DR and ME. Results from other investigations are considered more globally. According to several studies, age is an important risk factor. Consequently, a certain prevalence rate is reached at a shorter duration of NIDDM, in case NIDDM develops at an older age.

13.5 Visual Impairment

For reasons presented in section 10.5, the simulation model fixes the upper limit of visual impairment at 0.5, or 20/40, in the better eye. Unfortunately, findings on the prevalence of visual impairment are rather sporadic. An investigation by Klein and coworkers in the American state Wisconsin seems the most appropriate [84e].

	Females		Males		(own) Crosstabulation females by males	
Age	Number of patients	Prevalence of vision ≤ 20/40 in better eye	Number of patients	Prevalence of vision ≤ 20/40 in better eye	Pearson χ^2	Significance
30-44	142	0.0%	116	0.0%	—	—
45-54	337	7.3%	364	1.8%	12.1300	0.0005
55-64	767	4.2%	698	4.0%	0.0240	0.8769
65-74	949	11.3%	844	8.1%	5.2527	0.0219
75-84	593	27.6%	411	26.6%	0.1580	0.6910
≥ 85	125	48.7%	83	58.7%	2.0975	0.1475

Table 13.4 - Prevalence rates of visual impairment for NIDDM patients [Klein 84e]

The first five columns in table 13.4 borrow key statistics from this study. The prevalence rates concern visual impairment by any cause, whereas the simulation is strictly confined to effects of DR. The last two columns present results of our own crosstabulation analysis based on the four preceding columns. For two age groups, 45-54 years and 65-74 years, the prevalence of visual impairment is significantly higher among women than among men ($p < 0.05$). However, the remaining four age groups fail to reveal significant differences. Consequently, the simulation uses the same parameters for female and male patients to imitate the progression of visual impairment. The next chapter will nevertheless disclose striking dissimilarities between men and women caused by differences in life expectation. For any given age of onset, female patients have to face NIDDM during a longer period than male patients. This difference becomes relatively more important, if the age of onset increases. As a result, female patients receive considerably more ophthalmic care, especially in cohorts where NIDDM develops at the age of 75 years. For the same reason, the cumulative prevalence of visual impairment, like that of other disorders, is higher among female patients.

According to a diagram in the publication by Klein and associates, the prevalence of visual impairment does not exceed 20%, as long as the duration of diagnosed NIDDM is less than 20 years. Thereafter, the prevalence rises to more than 30%. This study does not present separate outcomes for NIDDM-a and NIDDM-b patients, as opposed to a four-year longitudinal investigation by Moss and associates in the American state Wisconsin [88]. According to the latter, the cumulative incidence of visual impairment was 16.1% among 423 NIDDM-a patients and 9.0% among 454 NIDDM-b patients. Initially, none of these 877 patients suffered from visual impairment, as defined earlier in this section.

These results cause uncertainty. The prevalence rates in the first study do not distinguish different medication types. The second investigation reveals that insulin taking patients are more likely to develop visual impairment. Unfortunately, the incidence rates found in this study provide insufficient support for relating the progression of visual impairment to the duration of NIDDM-a and NIDDM-b respectively. For that purpose, the study population should have been classified by *age* and by *age of onset.* This subdivision would result in rather small subpopulations, even if the number of age categories was limited to five or six. Therefore, these epidemiologic findings create a dilemma. While they indicate that differentiation is needed, they provide insufficient support to specify differentiated relationships. Consequently, the simulation is forced to use the same parameters for NIDDM-a and NIDDM-b. Furthermore, 33% of all cases of visual impairment among NIDDM patients result from DR. Cataract, glaucoma, and macular degeneration are responsible for the remaining 67%. For IDDM patients, 86% of all visual impairment is due to DR [Klein 84e]. As this investigation is confined to DR, the simulation uses conservative estimates for the prevalence of visual impairment among NIDDM patients.

13.6 Blindness

The epidemiologic findings presented in table 13.5 are the starting point for simulating the progression of blindness. They do not reveal significant differences between female and male patients. In the referenced article, a diagram relates the prevalence of blindness to the duration of diagnosed NIDDM without distinguishing different medication types. Less than 1% of all NIDDM patients younger than 80 years become blind during the first fifteen years after the diagnosis of NIDDM. The left part of table 13.5 relates the prevalence of blindness to the duration of NIDDM. The unit to the right distinguishes five age categories for patients who face diagnosed NIDDM for at least 15 years.

Number of years since onset of NIDDM	[Klein 84e] (N = 1370) Wisconsin United States
15-19	5% §
20-25	6% §

§ graph reading

Duration of NIDDM ≥ 15 year Age	[Klein 84e] (N = 1370) Wisconsin United States
45-54	4.5% §
55-64	3.5% §
65-74	3.8% §
75-84	7.0% §
≥ 85	11.8% §

Table 13.5 - Prevalence rates of blindness for NIDDM patients

An investigation from 1945 to 1969 of 1,060 NIDDM patients in Rochester (Minnesota, United States) by Dwyer and co-workers [85] related the cumulative incidence of blindness to the duration of diagnosed NIDDM. Within one year after the diagnosis of PDR, 38.1% of these patients became unilaterally blind and 7.1% bilaterally. In the absence of PDR, patients with DR were far less likely to become blind: the cumulative incidence of unilateral blindness equalled some 40% sixteen years after the diagnosis of NIDDM. For patients without DR, the corresponding percentage equalled ten according to graph reading. In a cross-sectional study of 503 Mexican patients by Paisey and associates [84b], five patients were blind and twenty visually impaired[2]. DR accounted for all cases of blindness and caused visual impairment in 18 of the 20 patients.

The progression of blindness is characterised by uncertainty, much like the course of visual impairment. The findings by Paisey and co-workers, for instance, conflict with the results by Klein and associates, which reveal that only 33% of all cases of visual impairment among NIDDM patients are due to DR [84e]. Moreover, at present there are insufficient statistics for differentiating the progression of blindness to the age of onset of NIDDM. Furthermore, the studies mentioned previously in this section point to prevalence differences between NIDDM-a and NIDDM-b without presenting precise epidemiologic data. Therefore, much uncertainty is involved in fixing the parameters that determine the progression of blindness in the simulation. Nonetheless, the course of blindness is the central issue of this simulation. In order to avoid excessive expectations on the effectiveness of ophthalmic care, the model uses conservative estimates. The results presented in the next chapter enable the reader to assess whether the simulation satisfies this objective.

2 This publication defines visual impairment as follows: *able to read large print only.*

13.7 Summary of Prevalence Rates

Table 13.6 presents the prevalence rates of retinal disorders and visual impairment that apply to the simulations for NIDDM patients. These rates are based on the epidemiologic data and the accompanying observations presented in previous sections.

	NIDDM-a		NIDDM-b	
	After 15 yr DM	Maximum	After 15 yr DM	Maximum
DR	85%	95%	58%	72%
ME	29%	38%	13%	28%
PDR	15%	32%	4%	15%
≤ 20/40	7%	14%	7%	14%
Blindness	3%	6%	3%	6%

Table 13.6 - Prevalence rates of retinal disorders and visual impairment

The previous sections have explained why the simulation distinguishes insulin taking and not-insulin taking patients. It may be relevant to add that a considerable number of NIDDM-b patients actually need insulin therapy for realising optimal metabolic management[3]. If inadequate metabolic control increases the likelihood of developing complications, this observation may justify to use the same prevalence rates of visual impairment and blindness for NIDDM-a and NIDDM-b patients.

3 verbal communication by prof.dr. F. Hendrikse, Professor of Ophthalmology, Department of Ophthalmology, University of Limburg School of Medicine, Maastricht

14

Results

14.1 Introduction

Succeeding sections present the principal outcomes of the simulations for NIDDM patients. The results may be divided into three groups. The first group includes epidemiologic findings: (a) the life expectation of NIDDM patients compared to the general population and (b) the prevalence rates of DR, ME, PDR, visual impairment and blindness. The second group comprises data on the volume of ophthalmic care in different scenarios, specified by the number of ophthalmic examinations, fluorescein angiograms and laser treatments. The third group relates to economic assessment. It comprises: (a) direct costs, (b) effects and benefits, and (c) average and marginal analyses. The simulation distinguishes three ages of onset (35, 55 and 75 years) besides two types of medication (insulin taking: NIDDM-a; not-insulin taking: NIDDM-b). Consequently, there are six times as many cohort simulations for NIDDM as for IDDM patients. They produce huge quantities of statistics. Without rigorous selections, the present chapter could easily grow out to an unacceptable size. This is avoided by presenting only the most important results after compression.

14.2 Life Expectation

Table 14.1 compares the life expectation of NIDDM patients to that of the general population in the Netherlands on the basis of hazard rates for 1983 to 1987 [CBS 88b:44-5]. The relative life expectation appears to increase, as the age of onset rises. This may be explained as follows. According to various investigations, the duration of NIDDM is the most important risk factor for the development and worsening of complications [Klein 84c; Hamman 89b; Nelson 89; Frank 91]. At a higher age of onset, NIDDM has less time to generate complications that reduce the relative life expectation [Panzram 87; Waugh 89].

			Females		Males	
			Life expectation in years at age 35			
		p	45.92	100.00%	39.78	100.00%
Age of onset 35 years	NIDDM-a	s0	34.68	75.51%	30.43	76.49%
		s1	34.86	75.92%	30.69	77.15%
		s2	35.19	76.63%	30.64	77.03%
		s3	35.11	76.45%	30.70	77.17%
		s4	35.34	76.96%	30.61	76.96%
	NIDDM-b	s0	36.11	78.64%	31.37	78.86%
		s1	36.17	78.76%	31.52	79.24%
		s2	36.41	79.28%	31.72	79.74%
		s3	36.56	79.61%	31.83	80.00%
		s4	36.48	79.43%	31.59	79.42%
			Life expectation in years at age 55			
		p	27.23	100.00%	21.57	100.00%
Age of onset 55 years	NIDDM-a	s0	21.39	78.54%	17.22	79.84%
		s1	21.44	78.75%	17.31	80.23%
		s2	21.36	78.45%	17.30	80.20%
		s3	21.47	78.86%	17.25	79.94%
		s4	21.49	78.93%	17.36	80.45%
	NIDDM-b	s0	21.98	80.72%	17.61	81.61%
		s1	21.87	80.31%	17.71	82.10%
		s2	22.03	80.90%	17.73	82.18%
		s3	22.00	80.81%	17.74	82.21%
		s4	22.22	81.61%	17.68	81.97%
			Life expectation in years at age 75			
		p	11.29	100.00%	8.45	100.00%
Age of onset 75 years	NIDDM-a	s0	9.16	81.10%	7.13	84.35%
		s1	9.13	80.88%	7.11	84.21%
		s2	9.19	81.37%	7.20	85.24%
		s3	9.11	80.65%	7.17	84.87%
		s4	9.13	80.84%	7.09	83.90%
	NIDDM-b	s0	9.27	82.13%	7.26	85.93%
		s1	9.32	82.58%	7.20	85.23%
		s2	9.30	82.39%	7.20	85.26%
		s3	9.25	81.96%	7.24	85.71%
		s4	9.32	82.54%	7.28	86.15%
p: general population; s0..s4: scenario 0..4						

Table 14.1 - Life expectation; option α

As the results are differentiated to age of onset, gender and scenario, table 14.1 enables thirty comparisons of NIDDM-a and NIDDM-b patients. For all cohorts of insulin taking patients, the life expectation is slightly smaller than for NIDDM-b cohorts. This is due to higher prevalence rates of retinal disorders for NIDDM-a patients.

The figures 11.1 to 11.2 in chapter 11 compare the life expectation of IDDM patients in five scenarios to that of the general population. They also want to give readers more insight into the way the simulation follows mortality. Obviously, it might be possible to present twelve similar diagrams for NIDDM patients. In cohorts where NIDDM develops at the age of 35 years, these diagrams reveal that the number of survivors follows a pattern which is similar to the pattern for IDDM patients, although the distances between the curves for diabetic patients and the general population are smaller. These distances decrease, as the age of onset increases. Furthermore, the twelve diagrams offer little information which is pertinent to this study. They are therefore omitted.

14.3 Prevalence of DR, ME, PDR, Visual Impairment and Blindness

For s0, the scenario without ophthalmic care, figure 14.1 and figure 14.2 picture the prevalence rates of DR, ME, PDR, visual impairment and blindness, by age. Both diagrams cumulate statistics of female and male patients who develop NIDDM at the age of 35 years. For NIDDM-a, the maximum prevalence rates of DR, ME and PDR are higher than for NIDDM-b. These maxima correspond to the percentages mentioned in table 3.2 (section 3.7) and in table 13.6 (section 13.7). Like the simulation for IDDM patients, the simulations for NIDDM patients approach the prevalence of blindness and visual impairment conservatively. The maximum prevalence rates of blindness correspond to the lowest percentages mentioned in table 13.5 (section 13.6). The maximum prevalence rates of visual impairment are considerably lower that the values presented in table 13.4 following observations in section 13.5. At the age of 75 years, the prevalence rate of visual impairment equals approximately 14% both for NIDDM-a and NIDDM-b patients, as indicated in figure 14.1 and figure 14.2.

This agrees with findings in Finland and the United States, where the prevalence of DM equals 10% to 19% for patients older than 65 years [Harris 87; Mykkänen 90; Wingard 90]. According to Morse and co-workers [86], DR causes visual impairment among 3% of the general population older than 75 years. Consequently, DR provokes visual impairment among at least 16% (= 3% / 19%) of all diabetic patients older than 75 years. This implies that the maxima in figure 14.1 and figure 14.2 are unlikely to overestimate the actual prevalence of visual impairment caused by DR.

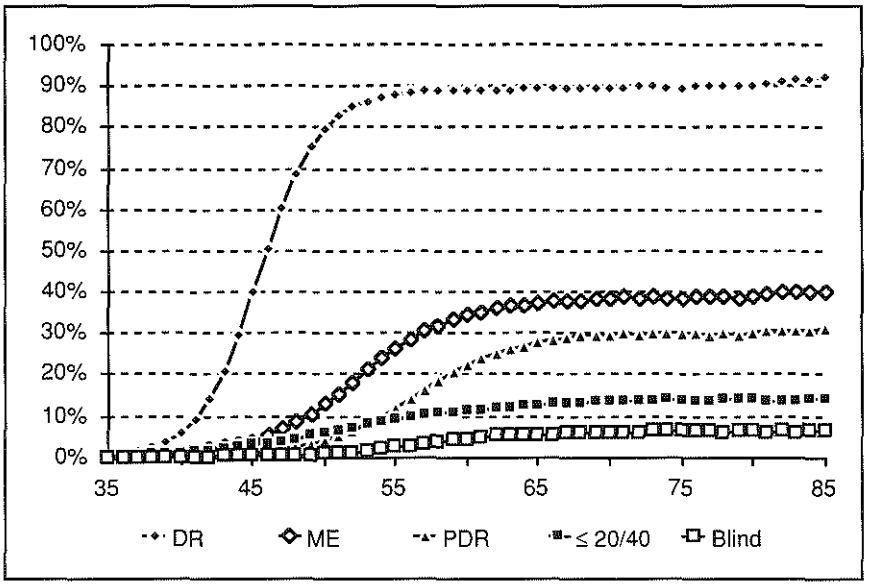

Figure 14.1 - Relative prevalence of retinopathy and visual impairment by age (years) scenario 0; NIDDM-a; age of onset 35 years; option α

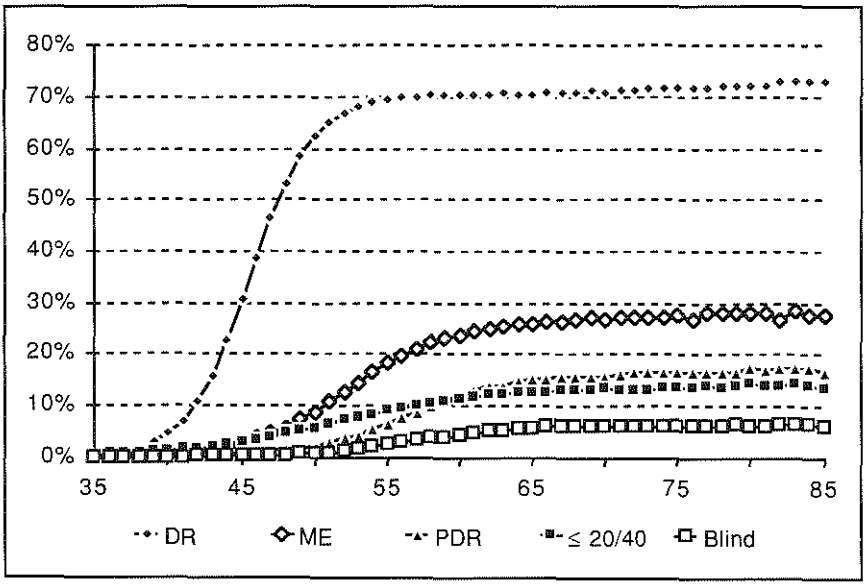

Figure 14.2 - Relative prevalence of retinopathy and visual impairment by age (years) scenario 0; NIDDM-b; age of onset 35 years; option α

Figure 14.3 and figure 14.4 present prevalence rates for cohorts where the age of onset equals 55 years. The maximum prevalence rates of the five disorders are approximately the same as in cohorts where NIDDM develops at the age of 35 years. The progression, related to the duration of NIDDM, offers a similar pattern. Figure 14.5 and figure 14.6 concern patients who develop NIDDM at the age of 75 years. As these diagrams cover a period of 20 years, the prevalence rates are unable to reach their maxima.

It seems reasonable to presume that DR is more likely to impede vision at older ages. This should lead to higher prevalence rates of visual impairment and blindness in cohorts where NIDDM develops at the age of 75 years. Figure 14.5 and figure 14.6 may create a surprise, because they fail to reveal this development. The following observations may offer an explanation. At older ages, the progression of vision among diabetic patients corresponds more and more to vision developments in the general population. Consequently, a relatively larger number of vision complaints by diabetic patients are due to cataract, glaucoma and senile macular degeneration [Klein 84e; Morse 86; Moss 88]. Given the delimitation of this investigation, the simulation model should only analyse blindness and visual impairment caused by DR. Vision disorders from other causes are not considered. For that reason, the model comprises no parameters or equations for relating the frequency of ophthalmic examinations to the onset of blindness and visual impairment caused by other eye diseases.

This delimitation may be subject of discussion. A higher frequency of ophthalmic examinations can contribute to an earlier diagnosis other eye disorders besides DR. Following the observations in the previous paragraph, this may interest elderly diabetic patients in particular. However, frequent ophthalmic examinations can hardly contribute to the timely diagnosis of cataract and senile macular degeneration, because patients usually discover symptoms in due time. Moreover, cataract surgery is one of the most successful ophthalmic techniques. It has been suggested however that the need for cataract surgery may be revealed earlier among diabetic patients, because they visit internists and ophthalmologists more frequently [Sommer 77]. So far, the fight against the adverse consequences of senile macular degeneration has been rather unsuccessful, although laser treatment is sometimes effective [MPSG 82]. Frequent ophthalmic examinations may contribute to timely diagnosing glaucoma, because chronic glaucoma fails to present early symptoms. Among these three disorders - cataract, senile macular degeneration, glaucoma - the first two occur at least ten times more frequently than the third [NEI 80; Leske 83; Morse 86]. Consequently, regular ophthalmic examinations can protect diabetic patients from blindness and visual impairment caused by disorders other than DM only to a smaller extent.

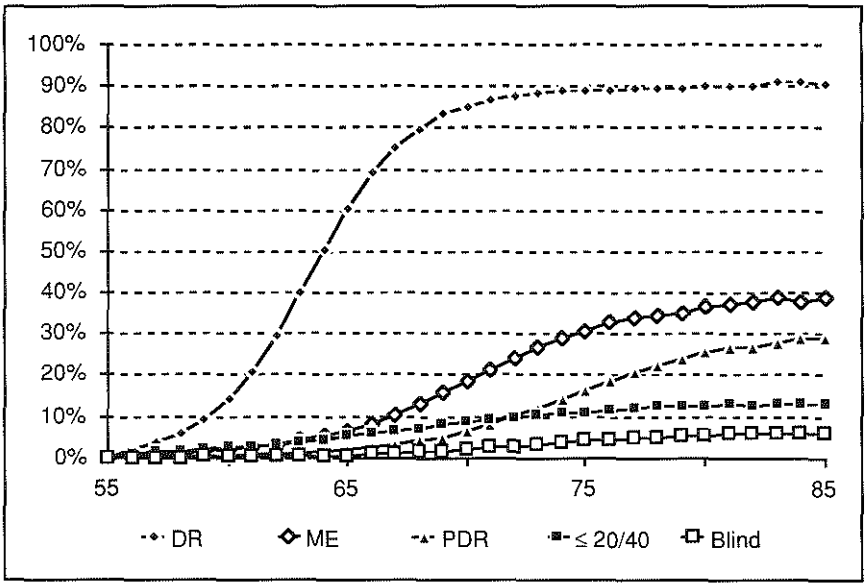

Figure 14.3 - Relative prevalence of retinopathy and visual impairment by age (years) scenario 0; NIDDM-a; age of onset 55 years; option α

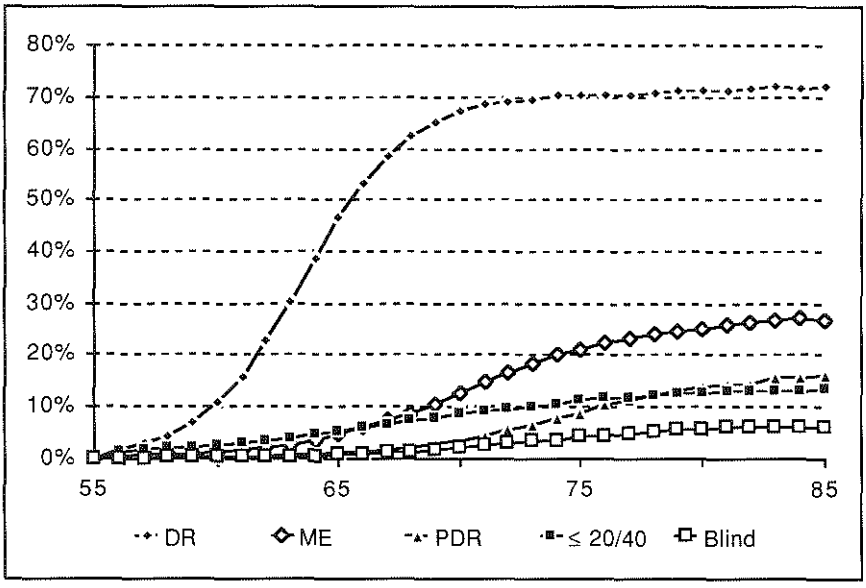

Figure 14.4 - Relative prevalence of retinopathy and visual impairment by age (years) scenario 0; NIDDM-b; age of onset 55 years; option α

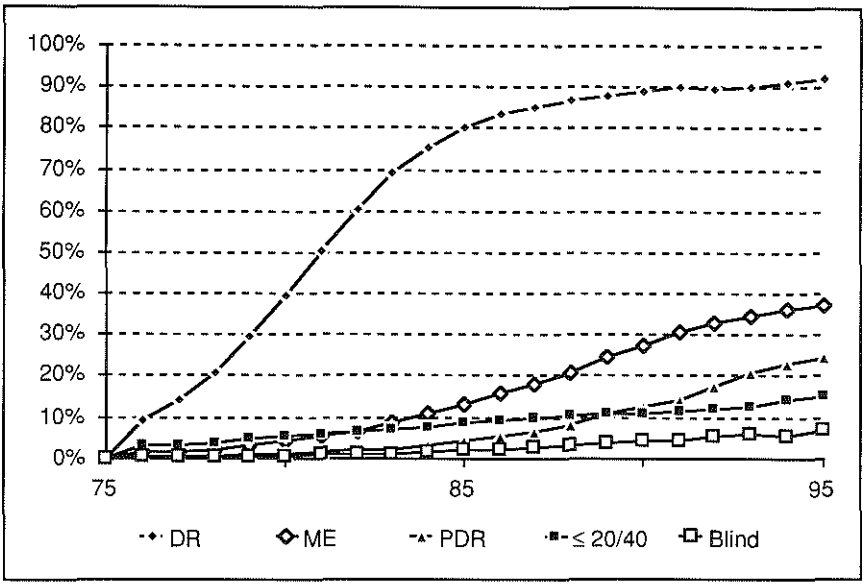

Figure 14.5 - Relative prevalence of retinopathy and visual impairment by age (years) scenario 0; NIDDM-a; age of onset 75 years; option α

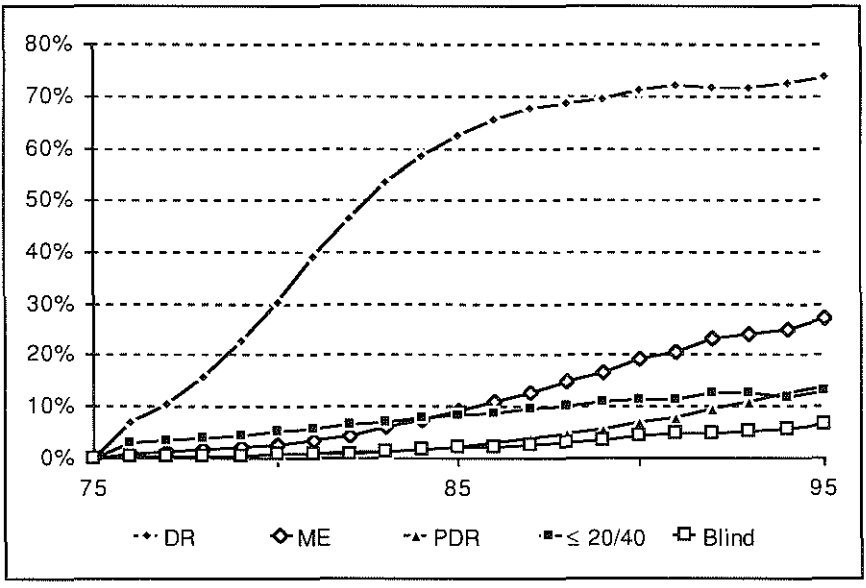

Figure 14.6 - Relative prevalence of retinopathy and visual impairment by age (years) scenario 0; NIDDM-b; age of onset 75 years; option α

		NIDDM-a				NIDDM-b			
		Females		Males		Females		Males	
Age of	s0	8953	100%	6489	100%	9642	100%	7173	100%
onset	s1	8539	95%	6184	95%	8710	90%	6491	90%
35 yrs	s2	7701	86%	5674	87%	7985	83%	5975	83%
	s3	7154	80%	4975	77%	7087	73%	5261	73%
	s4	6534	73%	4821	74%	6796	70%	5164	72%
Age of	s0	4077	100%	2469	100%	4313	100%	2655	100%
onset	s1	3783	93%	2302	93%	3969	92%	2442	92%
55 yrs	s2	3412	84%	2161	88%	3827	89%	2228	84%
	s3	3255	80%	1859	75%	3394	79%	2186	82%
	s4	2844	70%	1801	73%	3115	72%	1907	72%
Age of	s0	1012	100%	631	100%	1053	100%	692	100%
onset	s1	1046	103%	612	97%	1034	98%	645	93%
75 yrs	s2	943	93%	591	94%	1009	96%	655	95%
	s3	855	84%	564	89%	925	88%	624	90%
	s4	801	79%	526	83%	959	91%	603	87%

Table 14.2 - Cumulative prevalence of blindness (years and % of s0); option α

Table 14.2 presents the cumulative prevalence of blindness in all cohorts of NIDDM patients analysed by this simulation. As we already know, each cohort holds 10,000 patients initially. The comparison of the scenarios without ophthalmic care reveals that the cumulative prevalence of blindness is higher for NIDDM-b than for NIDDM-a patients. This has the following reason. For both medication types, the simulation uses the same parameters to describe the progression of blindness. The life expectation of NIDDM-b patients is slightly superior to that of NIDDM-a patients, as indicated in table 14.1. Following the differences in s0, NIDDM-a patients face less blindness than NIDDM-b patients in most of the four scenarios with ophthalmic care. Blindness occurs far more frequently among women than among men. Likewise, this is caused by differences in life expectation.

Table 14.2 also enables to compare three ages of onset. The cumulative prevalence of blindness due to DR decreases, as the age of onset rises. In cohorts where NIDDM develops at an older age, numerous patients pass away before prevalence rates reach their maximum. Furthermore, ophthalmic care prevents less blindness, both absolutely and relatively, at older ages of onset. The numbers in table 14.2, that illustrate the absolute decrease in prevention, need no further explanation.

IDDM	NIDDM		
Age of onset 15 yr	Age of onset 35 yr	Age of onset 55 yr	Age of onset 75 yr
39.4%	18.5%	17.7%	8.7%

Table 14.3 - Prevented blindness (average of percentages for s1..s4); option α

The four percentages in table 14.3 illustrate the relative decrease in prevention. They are determined as follows. Each of the three percentages for NIDDM corresponds to the unweighted average of 16 other percentages. The latter represent the prevented blindness in four scenarios, for men and women, as well as for NIDDM-a and NIDDM-b. These 16 percentages are directly derived from table 14.2. According to this table, ophthalmic care reduces the cumulative prevalence of blindness by 5%, 14%, 20% and 27% respectively in the four cohorts s1..s4 with female patients who develop NIDDM-a at the age of 35 years. Similarly, table 14.2 offers another 12 percentages for cohorts with the same age of onset, namely for male NIDDM-a patients as well as for female and male NIDDM-b patients. According to table 14.3, the unweighted average of these 16 percentages equals 18.5%. The percentage for IDDM in table 14.3 is determined analogously by the results presented in table 11.2 (section 11.3). However, this table presents results for eight cohorts with ophthalmic care: s1, s2, s3 and s4 for men and women separately. Therefore, 39.4% is the unweighted average of eight outcomes.

The percentages in table 14.3 confirm that ophthalmic care prevents comparatively less blindness at older ages of onset. How can this be explained? According to table 14.2, the cumulative prevalence of blindness equals 631 years in scenario zero for men who develop NIDDM-a at the age of 75 years. Ten years after the start of the simulation, the cumulative prevalence of blindness in this cohort equals more than 400 years, following other simulation results omitted in this chapter. The ratio of the cumulative prevalence at the end of the simulation and the cumulative prevalence after ten years of NIDDM has a much higher value for younger ages of onset. According to table 14.2, the cumulative prevalence equals 6,489 years in scenario zero at the end of the simulation for men who develop NIDDM-a at the age of 35 years. Ten years after the start of the simulation, the cumulative prevalence of blindness is less than 400 years (±6% of 6,489) in the same cohort. Therefore, at older ages of onset, most blindness results from the rapid progression of DR in a rather limited number of eyes. Blindness due to the slower progression of DR can only rarely materialise, as the life expectation is quite limited at older ages of onset. Ophthalmic care is less effective in combating the effects of rapid progressions of DR, because the retina is more likely to reach a state prohibiting successful laser treatment, when the patient has the next ophthalmic examination.

The results in table 14.2 confirm this. In cohorts where NIDDM develops at the age of 75 years, ophthalmic care prevents in scenario one on average some 2.3% of the blindness which occurs in scenario zero. This percentage is the unweigthed average of −3%, 3%, 2% and 7%. In younger onset cohorts (35 years), scenario one prevents 7.5% of the blindness related to scenario zero. The time interval between subsequent ophthalmic examinations equals eight years in this scenario for patients without DR. Rapid retinal deterioration may therefore remain unnoticed, until patients experience symptoms themselves and the optimum moment for laser treatment has elapsed too long ago. Consequently, substantial reductions of blindness due to DR among older onset patients require frequent ophthalmic care. If the age of onset is 75 years, the simulation results reveal for instance that the care intensity of scenario four is needed to prevent on average 15.0% of the blindness that occurs in scenario zero.

		NIDDM-a				NIDDM-b			
		Females		Males		Females		Males	
Age of	s0	25826	100%	20362	100%	27618	100%	21465	100%
onset	s1	25066	97%	19956	98%	27160	98%	21549	100%
35 yrs	s2	25333	98%	19921	98%	27294	99%	21457	100%
	s3	25076	97%	19406	95%	27276	99%	21385	100%
	s4	25147	97%	19411	95%	27217	99%	21285	99%
Age of	s0	14062	100%	9749	100%	14791	100%	10249	100%
onset	s1	13994	100%	9726	100%	14586	99%	10272	100%
55 yrs	s2	13677	97%	9782	100%	14790	100%	10177	99%
	s3	13775	98%	9533	98%	14763	100%	10268	100%
	s4	13794	98%	9742	100%	14794	100%	10166	99%
Age of	s0	5272	100%	3653	100%	5333	100%	3758	100%
onset	s1	5233	99%	3631	99%	5369	101%	3719	99%
75 yrs	s2	5258	100%	3653	100%	5356	100%	3766	100%
	s3	5168	98%	3617	99%	5306	99%	3766	100%
	s4	5207	99%	3639	100%	5457	102%	3809	101%

Table 14.4 - Cumulative prevalence of visual impairment (years and % of s0); option α

The results presented in table 14.4 indicate that ophthalmic care reduces the cumulative prevalence of visual impairment by 5% or less. Like the results for IDDM (cf. table 11.2 and table 11.3, section 11.4), the outcomes for NIDDM indicate that ophthalmic care is far more efficient in preventing blindness than milder types of visual impairment.

14.4 Ophthalmoscopy, Fluorescein Angiography and Photocoagulation

As indicated in table 14.5, patients with NIDDM-a receive far more ophthalmic examinations than patients with NIDDM-b, although the first have a lower life expectation. This difference results from the higher prevalence of retinal complications among patients with NIDDM-a. Furthermore, the number of ophthalmic examinations is roughly proportional to the intensity of ophthalmic care.

		NIDDM-a				NIDDM-b			
		Females		Males		Females		Males	
Age of	s1	86011	100%	72599	100%	79264	100%	66641	100%
onset	s2	176126	205%	146543	202%	160872	203%	135155	203%
35 yrs	s3	353149	411%	295415	407%	323727	408%	271667	408%
	s4	713773	830%	590287	813%	646217	815%	539015	809%
Age of	s1	48169	100%	36613	100%	44634	100%	34737	100%
onset	s2	96163	200%	73087	200%	89565	201%	68378	197%
55 yrs	s3	194547	404%	145034	396%	178354	400%	135752	391%
	s4	389671	809%	292914	800%	361021	809%	269902	777%
Age of	s1	19306	100%	15544	100%	18718	100%	15171	100%
onset	s2	36531	189%	28006	180%	34513	184%	26324	174%
75 yrs	s3	70708	366%	53153	342%	66235	354%	49838	329%
	s4	140755	729%	102107	657%	131471	702%	97247	641%

Table 14.5 - Cumulative number of ophthalmic examinations (% of s0); option α

To compare the number of ophthalmic examinations for men and women, the absolute results in table 14.5 were divided by the life expectation in table 14.1. According to these quotients, which are omitted in this chapter, the number of ophthalmic examinations is approximately proportional to life expectation. Nevertheless, women undergo slightly more examinations in relation to life expectation, as they have to face more retinal complications because of a higher life expectation. These quotients also enable to compare younger and older onset cohorts. As compared to life expectation, the number of ophthalmic examinations is the largest in cohorts where NIDDM develops at the age of 35 years. For the two other ages of onset, that number is on average 10% to 17% smaller.

		NIDDM-a				NIDDM-b			
		Females		Males		Females		Males	
Age of	s1	20140	100%	16640	100%	16408	100%	13287	100%
onset	s2	33891	168%	26453	159%	25610	156%	20662	156%
35 yrs	s3	56674	281%	44616	268%	38506	235%	30592	230%
	s4	99194	493%	76535	460%	63518	387%	50888	383%
Age of	s1	9618	100%	6543	100%	7780	100%	5120	100%
onset	s2	15778	164%	11252	172%	12004	154%	8518	166%
55 yrs	s3	23770	247%	15401	235%	16805	216%	11455	224%
	s4	37444	389%	23234	355%	24724	318%	16167	316%
Age of	s1	2432	100%	1494	100%	1662	100%	993	100%
onset	s2	4266	175%	2952	198%	3006	181%	1830	184%
75 yrs	s3	6332	260%	4477	300%	4279	257%	2848	287%
	s4	8105	333%	5603	375%	5717	344%	3785	381%

Table 14.6 - Cumulative number of fluorescein angiograms (% of s0); option α

Table 14.6 enables the reader to compare the number of fluorescein angiograms by different criteria. Regarding comparisons by type of medication or by gender, the previous observations for ophthalmic examinations are also relevant in this context. However, in contrast with ophthalmic examinations, increases in the intensity of ophthalmic care lead to less than proportional rises in the number of fluorescein angiograms. Moreover, the number of fluorescein angiograms decreases in relation to life expectation, as the age of onset increases. For cohorts where NIDDM develops at the age of 55 or 75 years, this number is on average 31%, respectively 60%, smaller than in the youngest onset cohorts. These differences result from the lower cumulative prevalence of retinal complications in relation to life expectation in older onset cohorts.

So far, this chapter has only presented results for option α, because the outcomes of option α and option β fail to reveal striking differences. As the frequency of fluorescein angiograms forms the characteristic distinction between these two options, one might expect a second table, besides table 14.6, representing the number of fluorescein angiograms for option β. However, the analysis for IDDM in part C reveals that the direct costs for the two options differ within relatively small margins. After adding *effects* and *benefits* to the economic analysis, the relative differences between the two options become even smaller. The results for NIDDM disclose the same tendency. Presenting the outcomes of two options would require much extra space without adding much information. Consequently, a choice is unavoidable. This chapter selects option α, because it generates marginally less favourable results regarding the cost-

effectiveness of ophthalmic care. This contributes to avoid overestimating auspicious consequences of ophthalmic care.

		NIDDM-a				NIDDM-b			
		Females		Males		Females		Males	
Age of	s1	5824	100%	5117	100%	3875	100%	3273	100%
onset	s2	7051	121%	6282	123%	4577	118%	4172	127%
35 yrs	s3	7472	128%	6764	132%	5089	131%	4553	139%
	s4	8099	139%	7252	142%	5461	141%	4854	148%
Age of	s1	3095	100%	1955	100%	1843	100%	1175	100%
onset	s2	4463	144%	3093	158%	2804	152%	1914	163%
55 yrs	s3	4955	160%	3428	175%	3177	172%	2148	183%
	s4	5282	171%	3740	191%	3581	194%	2499	213%
Age of	s1	628	100%	354	100%	363	100%	192	100%
onset	s2	1155	184%	703	199%	656	181%	391	204%
75 yrs	s3	1429	228%	929	262%	905	249%	494	257%
	s4	1720	274%	1088	307%	1068	294%	679	354%

Table 14.7 - Cumulative number of panretinal laser treatments (% of s0); option α

Table 14.7 shows that NIDDM-a patients receive far more panretinal laser treatments than NIDDM-b patients. This is due to the higher frequency of retinal disorders among NIDDM-a patients. Obviously, women have far more laser treatments than men because of a higher life expectation. The comparison of the four scenarios reveals that increases in the intensity of ophthalmic care generate less than proportionate rises in the number of laser treatments. This corresponds to outcomes for IDDM. However, as the age of onset increases, this growth discrepancy becomes less manifest. How can this be explained? Although more intensive ophthalmic care detects the need for laser treatment in shorter time, this need may ultimately also be discovered by a series of less frequent eye examinations. Therefore, at low hazard rates, the delay in detection caused by less frequent eye care hardly influences the cumulative number of laser treatments (cf. section 11.4). In older onset cohorts however, higher hazard rates prevail, when patients are due to receive laser treatment. Patients who would have received photocoagulation in a scenario of intensive eye care, are therefore more likely to pass away before the delayed detection in a scenario of less intensive ophthalmic care. Consequently, for older onset cohorts, the cumulative number of laser treatments diverges far more between various scenarios.

		NIDDM-a				NIDDM-b			
		Females		Males		Females		Males	
Age of	s1	1259	100%	1138	100%	1808	100%	1563	100%
onset	s2	2070	164%	1877	165%	2913	161%	2721	174%
35 yrs	s3	2765	220%	2658	234%	3815	211%	3573	229%
	s4	3175	252%	3017	265%	4197	232%	3941	252%
Age of	s1	1009	100%	772	100%	1099	100%	828	100%
onset	s2	1887	187%	1557	202%	2119	193%	1541	186%
55 yrs	s3	2715	269%	2342	303%	2995	273%	2392	289%
	s4	3115	309%	2658	344%	3565	324%	2816	340%
Age of	s1	442	100%	303	100%	337	100%	240	100%
onset	s2	987	223%	623	206%	763	226%	432	180%
75 yrs	s3	1603	363%	1124	371%	1345	399%	855	356%
	s4	2044	462%	1445	477%	1797	533%	1248	520%

Table 14.8 - Cumulative number of focal plus grid laser treatments (% of s0); option α

Table 14.8 presents the number of focal plus grid laser treatments. Women undergo far more laser treatments than men because of their higher life expectation. Apart from this foreseeable result, table 14.8 presents some unexpected outcomes. At the age of onset of 35 years, the number of treatments is larger for NIDDM-b than for NIDDM-a patients. The same observation applies to all cohorts - except for men in scenario two - where NIDDM develops at the age of 55 years. At the age of onset of 75 years however, NIDDM-a patients receive a larger number of treatments. These results are surprising, because the prevalence of ME has higher maxima for NIDDM-a than for NIDDM-b, according to table 3.2, table 13.2, figure 14.1 and figure 14.2. One would therefore expect the number of focal plus grid laser treatments to be greater for insulin taking patients.

The scheme *Screening and Treatment* presented in figure 8.11 (section 8.8) may indicate, why some results fail to meet these expectations. Following the guidelines of the simulation model, focal and grid laser treatments are confined to eyes with visual acuity between 0.1 and 0.6 (20/200 to 20/33). Furthermore, section 13.5 as well as the figures 14.1 to 14.6 indicate that the simulation uses the same parameters for NIDDM-a and NIDDM-b to imitate the progression of visual impairment. Moreover, the maximum prevalence of visual impairment is considerably smaller than that of ME. Consequently, the visual acuity of many eyes with ME is better than 0.6, or 20/33, so that these eyes are not eligible for focal or grid photocoagulation. Finally, NIDDM-a patients have a more limited life expectation than NIDDM-b patients, as table 14.1 indicates. These differences are larger in younger onset cohorts. In short, the cumulative

number of focal plus grid laser treatments depends on (1) the prevalence of ME, (2) the prevalence of visual impairment and (3) life expectation. Apparently, the two latter factors are predominant in cohorts where NIDDM develops at the age of 35 or 55 years.

When patients develop NIDDM at the age of 75 years, their life expectation equals 7.09 to 9.32 years (cf. table 14.1, section 14.2). During these years, the prevalence rates of visual impairment are on average at least as high as the prevalence rates of ME (cf. figure 14.5 and figure 14.6). Moreover, the simulation model closely correlates the progression of retinal disorders to vision deterioration, as indicated in section 7.6. Consequently, most patients (> 95% [1]) with ME also suffer from visual impairment. Only a small minority of these patients are excluded from focal or grid laser treatment, because their eyes fail to meet the vision requirements mentioned in the previous paragraph. For these patients, the factor *prevalence of ME* is a far more important determinant of the cumulative number of focal plus grid laser treatments than for younger onset patients. This explains why NIDDM-a patients receive more focal plus grid laser treatments than NIDDM-b patients in the oldest onset cohorts.

As ME occurs more frequently than PDR among NIDDM patients, one would expect these patients to receive more focal plus grid laser treatments than panretinal treatments. In table 14.7 and table 14.8 however, only the results for the oldest age of onset meet this expectation. The vision requirements for focal or grid laser treatments together with the relatively modest prevalence of visual impairment explain the discrepancy between the expected and the actual results for the two younger ages of onset.

14.5 Direct Costs

Table 14.9 records present values of the cumulative total direct costs for female plus male patients in option α. It distinguishes insulin and not-insulin taking patients, three discount rates, three ages of onset and four scenarios of ophthalmic care. The present values are determined at the start of the simulation in Dutch guilders (f). All amounts represent the sum of the costs for ophthalmic examinations, fluorescein angiograms and laser treatments (panretinal, focal and grid).

1 This percentage was derived from results omitted in this chapter.

			Annual discount rate		
			0%	5%	10%
NIDDM-a	Age of	s1	ƒ 42,734,667	ƒ 14,021,235	ƒ 5,986,502
	onset	s2	ƒ 64,589,112	ƒ 22,084,608	ƒ 9,745,306
	35 yrs	s3	ƒ 96,710,424	ƒ 33,611,633	ƒ 15,250,604
		s4	ƒ 130,498,090	ƒ 43,726,733	ƒ 19,423,275
	Age of	s1	ƒ 21,022,300	ƒ 9,450,890	ƒ 5,007,257
	onset	s2	ƒ 35,515,932	ƒ 16,276,599	ƒ 8,688,363
	55 yrs	s3	ƒ 51,339,521	ƒ 24,308,618	ƒ 13,417,133
		s4	ƒ 64,188,903	ƒ 30,174,894	ƒ 16,650,322
	Age of	s1	ƒ 5,798,026	ƒ 3,914,692	ƒ 2,856,432
	onset	s2	ƒ 11,133,608	ƒ 7,333,013	ƒ 5,183,620
	75 yrs	s3	ƒ 17,658,345	ƒ 11,907,976	ƒ 8,555,540
		s4	ƒ 21,774,960	ƒ 14,828,549	ƒ 10,756,203
NIDDM-b	Age of	s1	ƒ 34,358,835	ƒ 10,919,237	ƒ 4,677,691
	onset	s2	ƒ 52,973,684	ƒ 17,672,548	ƒ 7,816,213
	35 yrs	s3	ƒ 78,615,037	ƒ 26,818,559	ƒ 12,268,967
		s4	ƒ 101,577,957	ƒ 33,924,813	ƒ 15,337,963
	Age of	s1	ƒ 16,213,130	ƒ 7,244,774	ƒ 3,887,040
	onset	s2	ƒ 28,033,478	ƒ 12,660,313	ƒ 6,762,192
	55 yrs	s3	ƒ 41,578,426	ƒ 19,505,905	ƒ 10,772,075
		s4	ƒ 51,997,777	ƒ 24,321,460	ƒ 13,441,628
	Age of	s1	ƒ 4,321,844	ƒ 2,968,492	ƒ 2,214,695
	onset	s2	ƒ 8,108,501	ƒ 5,388,486	ƒ 3,857,946
	75 yrs	s3	ƒ 13,596,680	ƒ 9,114,436	ƒ 6,543,514
		s4	ƒ 17,438,993	ƒ 11,774,401	ƒ 8,488,162

Table 14.9 - Cumulative total direct costs; option α

The simulation discloses the disease progression during a longer period for younger than for older ages of onset. Therefore, positive discount rates affect the results of the youngest onset cohorts comparatively more than the outcomes of older onset cohorts. In all cases, the direct costs are larger for NIDDM-a than for NIDDM-b patients. This corresponds to the findings that insulin taking patients receive more ophthalmic examinations, fluorescein angiograms and panretinal laser treatments (cf. tables 14.5, 14.6 and 14.7, section 14.4). According to table 8.1 (section 8.4), the ophthalmic care intensity has the following proportion in the scenarios one to four: 1:2:4:8. According to table 14.9, quite a different proportion characterises the cumulative total direct costs. The increases in these costs are less than proportionate to the rises in the intensity of ophthalmic care. In common with IDDM (cf. table 11.9 and table 11.10 in section

11.5), the principal explanation is that the number of fluorescein angiograms and laser treatments have a lower growth rate than the intensity of ophthalmic care. At the age of onset of 35 years, this phenomenon is more distinct than at older ages of onset, but it is less explicit than for IDDM cohorts. patients. Considering both IDDM and NIDDM patients, the cumulative direct costs grow slower in relation to the intensity of ophthalmic care at lower ages of onset.

14.6 Effects and Benefits

Prevention of blindness and of other stages of visual impairment constitutes the principal objective of ophthalmic care. Section 11.6 suggested two measurement methods to assess the realisation of this objective: (1) *prevented vision loss* and (2) *realised sight gain*. The present analysis uses the same methods to evaluate the effects of ophthalmic care for NIDDM patients.

		NIDDM-a					NIDDM-b				
		s0	s1	s2	s3	s4	s0	s1	s2	s3	s4
		Realised sight gain (years)					Realised sight gain (years)				
ADR	s0		5261	9371	10360	12618		3661	9288	13415	10687
0%	s1	719		4110	5099	7357	1614		5627	9755	7027
	s2	2067	1348		989	3247	2854	1241		4128	1400
	s3	3313	2594	1246		2258	4467	2854	1613		-2728
	s4	4088	3369	2020	774		4854	3241	2000	387	
ADR	s0		1054	1710	2154	2622		681	1850	2649	2053
5%	s1	158		657	1101	1569	394		1169	1968	1372
	s2	537	379		444	912	726	332		799	203
	s3	898	740	361		468	1102	708	376		-596
	s4	1126	968	589	228		1246	851	519	144	
ADR	s0		295	372	568	718		202	523	703	533
10%	s1	35		77	273	423	128		321	502	331
	s2	165	130		196	346	238	110		181	10
	s3	289	254	124		150	337	209	99		-170
	s4	374	339	209	85		394	266	156	57	
		Prevented vision loss (years)					Prevented vision loss (years)				

Table 14.10 - Cumulative realised sight gain and prevented vision loss; 35 years; option α

Table 14.10 presents cumulative results for female plus male patients who develop NIDDM at the age of 35 years. The abbreviation ADR means *annual discount rate*. By

distinguishing two medication types and three discount rates, table 14.6 consists of six principal rectangular blocks, each containing two triangles. Upper triangles indicate *realised sight gain*, lower triangles *prevented vision loss*. At a discount rate of 0%, *prevented vision loss* corresponds to the results in table 14.2, apart from differences caused by rounding. Apparently, ophthalmic care prevents more blindness among NIDDM-b than among NIDDM-a patients. Section 14.3 gives an explanation for this outcome. *Realised sight gain* reaches a maximum of 13,415 years for NIDDM-b patients in scenario three at a discount rate of 0%. In insulin taking cohorts, the results reveal *"normal"* patterns: more intensive ophthalmic care always reduces the prevalence of blindness.

For not-insulin taking patients, scenario four presents a strikingly deviating result at a discount rate of 0%. Realised sight gain falls 2,728 years (= 13,415 – 10,687) short of the sight gain in scenario three. Table 14.1 (section 14.2) may explain this result. In scenario four, both female and male patients have a lower life expectation than in scenario three, so that less years allow realising sight gain. This result reveals limitations of this simulation technique. Apparently, a cohort size of 10,000 patients may not always exclude random disturbances which are characteristic for Monte Carlo simulations. This finding stresses that the global direction indicated by the results presented in this publication is more important than the results themselves. Furthermore, the absolute value of all numbers decreases at higher discount rates.

Table 14.11 has the same structure as table 14.10 and relates to patients who develop NIDDM at the age of 55 years. Seemingly, ophthalmic care is generally more effective for NIDDM-b than for NIDDM-a patients, at least at a discount rate of 0%. Nearly all results indicate that more intensive ophthalmic care enables to realise more sight gain and to prevent more vision loss. The transition from scenario one to scenario two for insulin taking patients presents an exception. The decrease in life expectation for female and male patients from scenario one to scenario two may offer an explanation (cf. table 14.1, section 14.2).

		NIDDM-a					NIDDM-b				
		s0	s1	s2	s3	s4	s0	s1	s2	s3	s4
		Realised sight gain (years)					Realised sight gain (years)				
ADR	s0		1856	1518	2524	4287		508	2654	2934	5170
0%	s1	461		-338	668	2432	557		2146	2426	4662
	s2	973	512		1006	2770	913	356		280	2516
	s3	1431	970	458		1764	1387	830	474		2236
	s4	1901	1440	928	470		1945	1388	1032	558	
ADR	s0		734	361	755	1330		235	771	832	1614
5%	s1	182		-373	21	596	214		536	598	1380
	s2	400	218		394	969	334	120		62	844
	s3	576	394	175		575	495	282	162		782
	s4	737	555	337	161		726	513	392	231	
ADR	s0		362	50	269	465		111	230	244	553
10%	s1	80		-312	-93	103	96		119	132	442
	s2	191	111		220	415	135	39		14	323
	s3	258	178	67		195	197	101	62		310
	s4	316	236	125	58		302	206	166	104	
		Prevented vision loss (years)					Prevented vision loss (years)				

Table 14.11 - Cumulative realised sight gain and prevented vision loss; 55 years; option α

Finally, table 14.12 presents the results for the oldest age of onset. As table 14.1 in section 14.2 indicates, the life expectation of these patients varies from some seven to some nine years. This time interval is too short to reach the maximum prevalence of blindness and visual impairment. This explains why table 14.12 mentions much smaller numbers than table 14.10 and table 14.11. Moreover, the simulation covers a much shorter period than simulations for younger onset cohorts. This increases the likelihood of random disturbances in mortality and prevalence patterns. Table 14.12 presents 29 negative and 31 positive results concerning realised sight gain. If the simulation imitates the actual progression of DR correctly, this implies that ophthalmic care can hardly prevent blindness caused by DR in the oldest onset cohort.

		NIDDM-a					NIDDM-b				
		s0	s1	s2	s3	s4	s0	s1	s2	s3	s4
		Realised sight gain (years)					Realised sight gain (years)				
ADR 0%	s0		-378	1167	152	-353		-652	-177	-176	836
	s1	-15		1545	530	25	-578		475	476	1487
	s2	110	124		-1015	-1520	83	660		1	1012
	s3	225	239	115		-505	197	775	115		1012
	s4	318	332	208	93		184	761	101	-14	
ADR 5%	s0		-277	738	34	-382		-622	-110	-197	543
	s1	-21		1015	311	-105	-551		512	425	1165
	s2	67	87		-704	-1120	40	591		-87	653
	s3	121	141	54		-416	110	661	70		740
	s4	172	193	106	52		106	657	66	-4	
ADR 10%	s0		-230	488	-25	-348		-594	-71	-182	383
	s1	-21		718	205	-118	-531		523	412	977
	s2	44	65		-513	-835	21	552		-111	454
	s3	66	88	22		-323	67	598	45		565
	s4	97	118	53	30		65	596	44	-1	
		Prevented vision loss (years)					Prevented vision loss (years)				

Table 14.12 - Cumulative realised sight gain and prevented vision loss; 75 years; option α

	Age of onset 35 years		Age of onset 55 years		Age of onset 75 years	
	Females	Males	Females	Males	Females	Males
NIDDM-a	0.8814	0.2926	0.4788	0.3716	0.1826	0.0053
NIDDM-b	0.8213	0.4512	0.5862	0.2942	0.0125	0.1329

Table 14.13 - R^2 for relation between intensity of ophthalmic care and life expectation (based on table 14.1, secion 14.2 [2])

This may also explain why results for younger onset cohorts, as compared to older onset cohorts, lead to a more prominent correlation between (x) the intensity of ophthalmic care and (y) the life expectation indicated by table 14.1 (section 14.2). A regression analysis of these two variables, x and y, provided some support for this rela-

2 These values of R^2 relate to the linear regression of (x) the values 0,1,2,3,4 and (y) the life expectations (in years) in the scenarios 0, 1, 2, 3 and 4. The choice of the x-values reflects a compromise between the actual proportion of the intensity of ophthalmic care expressed in ophthalmic examinations (0:1:2:4:8) and the proportion of the cumulative total costs in different scenarios. Each value of R^2 in table 14.13 is based on five points in a two-dimensional space. Therefore, the basis of this analysis is far too narrow for definite statements.

tionship. Table 14.13 presents the coefficients R^2 found by this analysis. However, these results should be considered quite cautiously for various technical reasons.

			Annual discount rate		
			0%	5%	10%
NIDDM-a	Age of	s1	ƒ 87,735,730	ƒ 20,670,214	ƒ 5,764,628
	onset	s2	ƒ 125,044,990	ƒ 34,287,607	ƒ 10,957,126
	35 yrs	s3	ƒ 188,810,904	ƒ 50,750,603	ƒ 16,264,492
		s4	ƒ 202,652,805	ƒ 58,420,601	ƒ 19,923,147
	Age of	s1	ƒ 17,910,670	ƒ 5,344,112	ƒ 1,393,444
	onset	s2	ƒ 45,754,498	ƒ 16,793,810	ƒ 6,774,220
	55 yrs	s3	ƒ 66,030,012	ƒ 24,907,262	ƒ 10,247,493
		s4	ƒ 67,876,342	ƒ 24,991,798	ƒ 9,624,608
	Age of	s1	ƒ 1,962,683	ƒ 1,176,780	ƒ 758,448
	onset	s2	ƒ 3,933,607	ƒ 2,775,964	ƒ 2,081,253
	75 yrs	s3	ƒ 9,222,650	ƒ 5,104,027	ƒ 2,961,421
		s4	ƒ 12,151,861	ƒ 7,005,298	ƒ 4,197,186
NIDDM-b	Age of	s1	ƒ 85,485,310	ƒ 19,301,541	ƒ 5,424,060
	onset	s2	ƒ 140,686,802	ƒ 36,408,577	ƒ 11,753,495
	35 yrs	s3	ƒ 196,460,774	ƒ 52,100,451	ƒ 16,650,306
		s4	ƒ 212,345,200	ƒ 54,624,015	ƒ 17,249,955
	Age of	s1	ƒ 18,313,285	ƒ 5,487,274	ƒ 1,601,589
	onset	s2	ƒ 31,420,946	ƒ 12,111,898	ƒ 5,431,493
	55 yrs	s3	ƒ 44,726,048	ƒ 16,038,511	ƒ 6,540,986
		s4	ƒ 54,854,793	ƒ 21,715,332	ƒ 9,564,132
	Age of	s1	ƒ 2,859,897	ƒ 1,850,386	ƒ 1,314,992
	onset	s2	ƒ 4,351,708	ƒ 2,498,667	ƒ 1,585,751
	75 yrs	s3	ƒ 9,328,125	ƒ 5,656,743	ƒ 3,741,861
		s4	ƒ 4,831,368	ƒ 2,637,956	ƒ 1,533,016

Table 14.14 - Cumulative total benefits; option α

According to section 9.7, the simulation distinguishes direct and indirect benefits: (1) savings in disability facilities and (2) savings in production losses. They are not mentioned separately to save space. Each amount in table 14.14 represents the sum of direct and indirect benefits. Savings in production losses were determined by the *human capital approach*. As table 14.14 presents 36 results both for NIDDM-a and NIDDM-b, it allows 36 comparisons in pairs. The ratio of the two outcomes varies between 0.577 and 2.738, so that the result for NIDDM-a may be 32% smaller to 174% larger than the corresponding result for NIDDM-b. This spread is surprising, because the simula-

tion uses the same parameters to imitate the progression of blindness and visual impairment for both medication types.

These differences require further analysis. The three largest upward outliers relate to scenario four and the age of onset of 75 years. After disregarding these three outliers, thirty three comparisons in pairs remain where the NIDDM-a result is, at the most, 57% larger than the NIDDM-b result. To a degree, these differences result from random fluctuations. Therefore, it seems sensible to group the outcomes for aggregated comparisons. If all results for the age of onset of 35 years are included in one comparison, the cumulative total benefits for NIDDM-a are 0.1% larger than for NIDDM-b. For the ages of onset of 55 and 75 years, the cumulative total benefits are 24%, respectively 32%, larger for NIDDM-a. Furthermore, the sum of all the 36 results for NIDDM-a is 5% larger than the corresponding sum for NIDDM-b.

Do these findings correspond to the starting points of the simulation? Considering all cohorts of the youngest onset patients, insulin taking is on average associated with a 3% decrease in life expectation following the results in table 14.1 (section 14.2). Moreover, NIDDM-a patients receive some 50% more panretinal laser treatments (cf. table 14.7, section 14.4) and 27% less focal plus grid laser treatments (cf. table 14.8, section 14.4). As the latter concern central acuity, it is not surprising that 26% less vision loss is prevented at a discount rate of 0% in the scenarios one to four among NIDDM-a patients, as compared to NIDDM-b patients (cf. table 14.10). As opposed to this, the results reveal 2% more realised sight gain in NIDDM-a cohorts. Ophthalmic care prevents more visual impairment among NIDDM-a than among NIDDM-b patients (table 14.4, section 14.3). As the prevention of blindness is more effective for NIDDM-b, and the prevention of visual impairment for NIDDM-a, it seems reasonable that the cumulative total benefits differ only within narrow margins for both types of medication.

In the oldest age of onset cohorts, insulin taking patients receive 69% more panretinal and 22% more focal plus grid laser treatments than NIDDM-b patients (cf. table 14.7 and table 14.8, section 14.4). Following the presumptions of the simulation model, a certain fraction of these treatments is effective. Therefore, more sight gain may be realised among NIDDM-a patients. The first line of table 14.12 confirms this. The total realised sight gain in the scenarios one to four equals +589 years for NIDDM-a and −168 years for NIDDM-b. However, life expectation is more than 1% shorter for insulin taking patients. As the cumulative total benefits for NIDDM-a are 32% larger than for NIDDM-b, the difference in realised sight gain has more weight than the difference

in life expectation, which seems quite acceptable considering the previously mentioned results.

The foregoing observations support the assertion that the results in table 14.14 correspond broadly to the epidemiologic basis of the simulation, at least for cohorts where NIDDM develops at the age of 35 or 75 years. However, for the 55 years onset cohorts, the results disagree with this assertion. Insulin taking patients receive 57% more panretinal and 8% less focal plus grid laser treatments than NIDDM-b patients (cf. table 14.7 and table 14.8, section 14.4), which is followed by 1% more prevented vision loss and 11% more realised sight gain for NIDDM-b patients, at a discount rate of 0%. This result may be explained by the 2.5% lower life expectation of insulin taking patients (cf. table 14.1, section 14.2). Although ophthalmic care is more effective in preventing vision loss and in realising sight gain for NIDDM-b, the cumulative total benefits are 24% larger for NIDDM-a. This outcome can only be explained by the smaller prevalence of visual impairment for NIDDM-a (cf. table 14.4, section 14.3). However, the results presented in this chapter do not provide insight into the distribution of visual impairment over various vision categories. In the last resort, this distribution determines the cumulative total benefits.

14.7 Average and Marginal Analysis

Table 14.15 comprises the blocks A and B. Block A presents ratios of cumulative total direct costs and realised sight gain, whereas block B displays ratios of cumulative total direct costs and prevented vision loss. All the ratios in table 14.15 may be considered as the average or the marginal direct costs needed to realise one year sight gain (block A) or to prevent one year vision loss (block B). The results are derived from the tables 14.9 to 14.12 before the numbers in the tables 14.10 to 14.12 were rounded to integers. Each rectangle with results presents seven ratios. The upper four indicate average costs, the lower three marginal costs, following the technique introduced in section 11.7. Table 14.15 presents a large number of ratios for the sake of completeness. Which tendency do these statistics disclose?

			NIDDM-a			NIDDM-b		
			Annual discount rate			Annual discount rate		
			0%	5%	10%	0%	5%	10%
A	Age of	s0 -> s1	ƒ 8,124	ƒ 13,308	ƒ 20,320	ƒ 9,386	ƒ 16,038	ƒ 23,165
	onset	s0 -> s2	ƒ 6,893	ƒ 12,913	ƒ 26,224	ƒ 5,704	ƒ 9,553	ƒ 14,948
	35 yrs	s0 -> s3	ƒ 9,335	ƒ 15,602	ƒ 26,854	ƒ 5,860	ƒ 10,125	ƒ 17,441
		s0 -> s4	ƒ 10,343	ƒ 16,676	ƒ 27,062	ƒ 9,505	ƒ 16,527	ƒ 28,775
		s1 -> s2	ƒ 5,317	ƒ 12,279	ƒ 48,809	ƒ 3,308	ƒ 5,777	ƒ 9,779
		s2 -> s3	ƒ 32,470	ƒ 25,953	ƒ 28,048	ƒ 6,212	ƒ 11,447	ƒ 24,662
		s3 -> s4	ƒ 14,965	ƒ 21,624	ƒ 27,848	-ƒ 8,417	-ƒ 11,921	-ƒ 18,009
	Age of	s0 -> s1	ƒ 11,330	ƒ 12,876	ƒ 13,833	ƒ 31,931	ƒ 30,853	ƒ 34,956
	onset	s0 -> s2	ƒ 23,404	ƒ 45,025	ƒ 174,870	ƒ 10,565	ƒ 16,426	ƒ 29,380
	55 yrs	s0 -> s3	ƒ 20,345	ƒ 32,176	ƒ 49,838	ƒ 14,172	ƒ 23,431	ƒ 44,203
		s0 -> s4	ƒ 14,973	ƒ 22,684	ƒ 35,840	ƒ 10,058	ƒ 15,065	ƒ 24,287
		s1 -> s2	-ƒ 42,881	-ƒ 18,324	-ƒ 11,788	ƒ 5,509	ƒ 10,105	ƒ 24,168
		s2 -> s3	ƒ 15,729	ƒ 20,386	ƒ 21,541	ƒ 48,332	ƒ 110,883	ƒ 296,344
		s3 -> s4	ƒ 7,286	ƒ 10,207	ƒ 16,550	ƒ 4,660	ƒ 6,158	ƒ 8,618
	Age of	s0 -> s1	-ƒ 15,339	-ƒ 14,125	-ƒ 12,412	-ƒ 6,634	-ƒ 4,775	-ƒ 3,731
	onset	s0 -> s2	ƒ 9,538	ƒ 9,938	ƒ 10,631	-ƒ 45,941	-ƒ 49,069	-ƒ 54,620
	75 yrs	s0 -> s3	ƒ 115,983	ƒ 352,780	-ƒ 340,233	-ƒ 77,254	-ƒ 46,367	-ƒ 36,008
		s0 -> s4	-ƒ 61,729	-ƒ 38,841	-ƒ 30,936	ƒ 20,866	ƒ 21,668	ƒ 22,144
		s1 -> s2	ƒ 3,453	ƒ 3,368	ƒ 3,242	ƒ 7,972	ƒ 4,728	ƒ 3,142
		s2 -> s3	-ƒ 6,428	-ƒ 6,497	-ƒ 6,576	ƒ 10,976,359	-ƒ 42,946	-ƒ 24,175
		s3 -> s4	-ƒ 8,152	-ƒ 7,029	-ƒ 6,823	ƒ 3,798	ƒ 3,595	ƒ 3,442
B	Age of	s0 -> s1	ƒ 59,436	ƒ 88,696	ƒ 169,129	ƒ 21,295	ƒ 27,687	ƒ 36,540
	onset	s0 -> s2	ƒ 31,244	ƒ 41,114	ƒ 59,043	ƒ 18,560	ƒ 24,332	ƒ 32,905
	35 yrs	s0 -> s3	ƒ 29,189	ƒ 37,433	ƒ 52,694	ƒ 17,598	ƒ 24,334	ƒ 36,421
		s0 -> s4	ƒ 31,926	ƒ 38,825	ƒ 51,939	ƒ 20,926	ƒ 27,234	ƒ 38,954
		s1 -> s2	ƒ 16,209	ƒ 21,271	ƒ 28,990	ƒ 15,003	ƒ 20,346	ƒ 28,655
		s2 -> s3	ƒ 25,780	ƒ 31,953	ƒ 44,269	ƒ 15,897	ƒ 24,338	ƒ 44,830
		s3 -> s4	ƒ 43,639	ƒ 44,296	ƒ 49,352	ƒ 59,336	ƒ 49,493	ƒ 53,959
	Age of	s0 -> s1	ƒ 45,651	ƒ 51,931	ƒ 62,608	ƒ 29,095	ƒ 33,929	ƒ 40,479
	onset	s0 -> s2	ƒ 36,520	ƒ 40,655	ƒ 45,487	ƒ 30,705	ƒ 37,950	ƒ 50,007
	55 yrs	s0 -> s3	ƒ 35,883	ƒ 42,216	ƒ 52,086	ƒ 29,972	ƒ 39,386	ƒ 54,635
		s0 -> s4	ƒ 33,770	ƒ 40,935	ƒ 52,677	ƒ 26,731	ƒ 33,498	ƒ 44,579
		s1 -> s2	ƒ 28,308	ƒ 31,258	ƒ 33,154	ƒ 33,227	ƒ 45,103	ƒ 73,346
		s2 -> s3	ƒ 34,530	ƒ 45,778	ƒ 71,018	ƒ 28,561	ƒ 42,349	ƒ 64,740
		s3 -> s4	ƒ 27,339	ƒ 36,363	ƒ 55,276	ƒ 18,673	ƒ 20,864	ƒ 25,579
	Age of	s0 -> s1	-ƒ 399,864	-ƒ 189,923	-ƒ 134,393	-ƒ 7,484	-ƒ 5,389	-ƒ 4,171
	onset	s0 -> s2	ƒ 101,445	ƒ 110,198	ƒ 118,299	ƒ 98,285	ƒ 133,684	ƒ 179,692
	75 yrs	s0 -> s3	ƒ 78,569	ƒ 98,819	ƒ 129,019	ƒ 68,931	ƒ 82,736	ƒ 98,254
		s0 -> s4	ƒ 68,583	ƒ 86,073	ƒ 111,154	ƒ 94,906	ƒ 110,745	ƒ 130,314
		s1 -> s2	ƒ 42,942	ƒ 39,221	ƒ 35,763	ƒ 5,737	ƒ 4,094	ƒ 2,975
		s2 -> s3	ƒ 56,737	ƒ 84,785	ƒ 149,901	ƒ 47,827	ƒ 53,338	ƒ 59,510
		s3 -> s4	ƒ 44,384	ƒ 56,409	ƒ 72,256	-ƒ 284,616	-ƒ 692,167	-ƒ 1,330,362

Table 14.15 - Direct costs related to realised sight gain and prevented vision loss; option α

			NIDDM-a			NIDDM-b		
			Annual discount rate			Annual discount rate		
			0%	5%	10%	0%	5%	10%
A	Age of onset 35 yrs	s0 -> s1	-f 8,555	-f 6,311	f 753	-f 13,966	-f 12,312	-f 3,696
		s0 -> s2	-f 6,452	-f 7,135	-f 3,261	-f 9,444	-f 10,128	-f 7,530
		s0 -> s3	-f 8,890	-f 7,955	-f 1,785	-f 8,784	-f 9,544	-f 6,228
		s0 -> s4	-f 5,719	-f 5,604	-f 696	-f 10,364	-f 10,084	-f 3,587
		s1 -> s2	-f 3,760	-f 8,458	-f 18,617	-f 6,502	-f 8,857	-f 9,942
		s2 -> s3	-f 31,988	-f 11,113	f 1,008	-f 7,300	-f 8,193	-f 2,459
		s3 -> s4	f 8,834	f 5,227	f 3,430	-----	-----	-----
	Age of onset 55 yrs	s0 -> s1	f 1,677	f 5,595	f 9,984	-f 4,136	f 7,485	f 20,553
		s0 -> s2	-f 6,747	-f 1,431	f 38,526	-f 1,277	f 712	f 5,782
		s0 -> s3	-f 5,821	-f 792	f 11,774	-f 1,073	f 4,165	f 17,362
		s0 -> s4	-f 860	f 3,896	f 15,123	-f 553	f 1,614	f 7,006
		s1 -> s2	-----	-----	-----	-f 600	-f 2,256	-f 8,025
		s2 -> s3	-f 4,425	-f 207	f 5,719	f 856	f 47,281	f 214,349
		s3 -> s4	f 6,239	f 10,060	f 19,738	f 130	-f 1,101	-f 1,142
	Age of onset 75 yrs	s0 -> s1	-----	-----	-----	-----	-----	-----
		s0 -> s2	f 6,168	f 6,176	f 6,362	-----	-----	-----
		s0 -> s3	f 55,407	f 201,571	-----	-----	-----	-----
		s0 -> s4	-----	-----	-----	f 15,085	f 16,813	f 18,145
		s1 -> s2	f 2,177	f 1,792	f 1,399	f 4,831	f 3,461	f 2,624
		s2 -> s3	-----	-----	-----	f 1,023,525	-----	-----
		s3 -> s4	-----	-----	-----	f 8,242	f 7,674	f 7,351
B	Age of onset 35 yrs	s0 -> s1	-f 62,588	-f 42,061	f 6,268	-f 31,687	-f 21,254	-f 5,830
		s0 -> s2	-f 29,245	-f 22,718	-f 7,342	-f 30,731	-f 25,796	-f 16,575
		s0 -> s3	-f 27,798	-f 19,088	-f 3,503	-f 26,380	-f 22,940	-f 13,006
		s0 -> s4	-f 17,653	-f 13,047	-f 1,337	-f 22,819	-f 16,617	-f 4,856
		s1 -> s2	-f 11,463	-f 14,652	-f 11,057	-f 29,488	-f 31,193	-f 29,134
		s2 -> s3	-f 25,397	-f 13,683	f 1,592	-f 18,681	-f 17,419	-f 4,471
		s3 -> s4	f 25,761	f 10,708	f 6,079	f 18,291	f 31,917	f 43,416
	Age of onset 55 yrs	s0 -> s1	f 6,757	f 22,566	f 45,185	-f 3,769	f 8,231	f 23,801
		s0 -> s2	-f 10,528	-f 1,292	f 10,021	-f 3,710	f 1,644	f 9,841
		s0 -> s3	-f 10,268	-f 1,040	f 12,305	-f 2,269	f 7,001	f 21,460
		s0 -> s4	-f 1,940	f 7,031	f 22,227	-f 1,469	f 3,589	f 12,860
		s1 -> s2	-f 26,075	-f 21,175	-f 15,308	-f 3,619	-f 10,070	-f 24,356
		s2 -> s3	-f 9,715	-f 464	f 18,855	f 506	f 18,058	f 46,827
		s3 -> s4	f 23,411	f 35,839	f 65,925	f 521	-f 3,732	-f 3,388
	Age of onset 75 yrs	s0 -> s1	-----	-----	-----	-----	-----	-----
		s0 -> s2	f 65,604	f 68,482	f 70,801	f 45,537	f 71,694	f 105,832
		s0 -> s3	f 37,534	f 56,463	f 84,360	f 21,640	f 31,387	f 42,068
		s0 -> s4	f 30,309	f 45,411	f 67,780	f 68,613	f 85,933	f 106,779
		s1 -> s2	f 27,080	f 20,872	f 15,435	f 3,477	f 2,997	f 2,485
		s2 -> s3	f 10,745	f 41,641	f 110,772	f 4,460	f 8,129	f 11,732
		s3 -> s4	f 12,802	f 19,687	f 31,681	-----	-----	-----

Table 14.16 - Direct costs, benefits, realised sight gain, and prevented vision loss; option α

The average costs per year realised sight gain or prevented vision loss increase, as the age of onset rises. For the oldest onset cohorts, some ratios are negative, because extra ophthalmic care leads to less sight gain or more vision loss. The average costs increase, while the discount rate rises. In other words, costs precede effects and benefits in time. The comparison of NIDDM-a and NIDDM-b fails to unfold a distinct tendency. In most cases, the average costs per year realised sight gain (block A) are smaller than the corresponding average costs per year prevented vision loss (block B). The ratios presented in section 11.7 for IDDM patients are in tune with the foregoing observations. Furthermore, the numbers of outliers increases, as the age of onset rises.

The ratios in table 14.16 are derived from the results in the tables 14.9 to 14.14, apart from table 14.13. They correspond to quotient 14.1. Negative numerators indicate that the cumulative total direct costs are smaller than the total benefits, comprising savings in disability facilities and production losses, the latter determined by the *human capital approach.*

$$\frac{\text{total direct costs} - \text{production growth} - \text{disability facilities savings}}{\text{realised sight gain or prevented vision loss}} \qquad (14.1)$$

In most cases, the denominator of this quotient is positive. However, the tables 14.10 to 14.12 disclose some negative effects. They create ambiguity, as section 11.7 has demonstrated. To avoid confusion, the presentation of results by the tables 14.16 and 14.17 is confined to positive outcomes of ophthalmic care, indicated by a positive denominator. Vacant positions reflect negative medical outcomes. If costs exceed benefits, a positive result appears. Negative values indicate experiences which are desirable both for medical and financial reasons.

For the youngest age of onset, all ratios in table 14.16 concerning the average analysis are negative, apart from the ratio for NIDDM-a in scenario one at a discount rate of 10%. Ophthalmic care is nearly always characterised by a favourable balance of costs and benefits. Less favourable results appear for cohorts where NIDDM develops at the age of 55 years. Most results concerning the average analysis are positive at a discount rate of 5% or 10%. For the oldest onset cohorts, table 14.16 omits a larger number of results, because medical effects are frequently negative. One year prevented vision loss costs at least *f* 31,387 at a discount rate of 5%.

			NIDDM-a			NIDDM-b		
			Annual discount rate			Annual discount rate		
			0%	5%	10%	0%	5%	10%
A	Age of	s0 -> s1	ƒ 5,818	ƒ 10,635	ƒ 17,711	ƒ 5,162	ƒ 10,800	ƒ 17,934
	onset	s0 -> s2	ƒ 4,610	ƒ 9,577	ƒ 21,407	ƒ 2,842	ƒ 5,922	ƒ 10,804
	35 yrs	s0 -> s3	ƒ 6,235	ƒ 11,580	ƒ 21,923	ƒ 3,006	ƒ 6,458	ƒ 13,127
		s0 -> s4	ƒ 7,410	ƒ 12,694	ƒ 22,130	ƒ 5,645	ƒ 11,368	ƒ 22,448
		s1 -> s2	ƒ 3,063	ƒ 7,880	ƒ 35,545	ƒ 1,333	ƒ 3,081	ƒ 6,318
		s2 -> s3	ƒ 21,625	ƒ 19,294	ƒ 22,901	ƒ 3,374	ƒ 7,698	ƒ 19,856
		s3 -> s4	ƒ 12,805	ƒ 17,824	ƒ 22,915	-----	-----	-----
	Age of	s0 -> s1	ƒ 9,590	ƒ 11,342	ƒ 12,657	ƒ 24,818	ƒ 25,716	ƒ 30,917
	onset	s0 -> s2	ƒ 18,448	ƒ 37,062	ƒ 149,785	ƒ 8,226	ƒ 13,444	ƒ 25,150
	55 yrs	s0 -> s3	ƒ 15,949	ƒ 26,471	ƒ 42,933	ƒ 11,047	ƒ 19,517	ƒ 38,828
		s0 -> s4	ƒ 11,931	ƒ 18,933	ƒ 31,356	ƒ 7,767	ƒ 12,298	ƒ 20,886
		s1 -> s2	-----	-----	-----	ƒ 4,300	ƒ 8,067	ƒ 19,760
		s2 -> s3	ƒ 12,178	ƒ 16,753	ƒ 18,750	ƒ 37,756	ƒ 95,342	ƒ 271,481
		s3 -> s4	ƒ 6,181	ƒ 9,025	ƒ 15,403	ƒ 3,463	ƒ 4,612	ƒ 6,771
	Age of	s0 -> s1	-----	-----	-----	-----	-----	-----
	onset	s0 -> s2	ƒ 8,888	ƒ 9,285	ƒ 9,964	-----	-----	-----
	75 yrs	s0 -> s3	ƒ 105,722	ƒ 326,914	-----	-----	-----	-----
		s0 -> s4	-----	-----	-----	ƒ 19,628	ƒ 20,617	ƒ 21,266
		s1 -> s2	ƒ 3,063	ƒ 2,957	ƒ 2,815	ƒ 7,556	ƒ 4,587	ƒ 3,097
		s2 -> s3	-----	-----	-----	ƒ 9,525,646	-----	-----
		s3 -> s4	-----	-----	-----	ƒ 4,073	ƒ 3,848	ƒ 3,694
B	Age of	s0 -> s1	ƒ 42,568	ƒ 70,881	ƒ 147,415	ƒ 11,713	ƒ 18,644	ƒ 28,289
	onset	s0 -> s2	ƒ 20,896	ƒ 30,493	ƒ 48,197	ƒ 9,249	ƒ 15,083	ƒ 23,782
	35 yrs	s0 -> s3	ƒ 19,495	ƒ 27,785	ƒ 43,019	ƒ 9,027	ƒ 15,521	ƒ 27,413
		s0 -> s4	ƒ 22,875	ƒ 29,555	ƒ 42,474	ƒ 12,428	ƒ 18,733	ƒ 30,389
		s1 -> s2	ƒ 9,339	ƒ 13,650	ƒ 21,112	ƒ 6,046	ƒ 10,851	ƒ 18,515
		s2 -> s3	ƒ 17,169	ƒ 23,754	ƒ 36,146	ƒ 8,634	ƒ 16,368	ƒ 36,095
		s3 -> s4	ƒ 37,339	ƒ 36,512	ƒ 40,609	ƒ 51,682	ƒ 43,386	ƒ 48,018
	Age of	s0 -> s1	ƒ 38,640	ƒ 45,745	ƒ 57,284	ƒ 22,613	ƒ 28,280	ƒ 35,802
	onset	s0 -> s2	ƒ 28,787	ƒ 33,465	ƒ 38,962	ƒ 23,907	ƒ 31,061	ƒ 42,808
	55 yrs	s0 -> s3	ƒ 28,130	ƒ 34,731	ƒ 44,870	ƒ 23,361	ƒ 32,808	ƒ 47,991
		s0 -> s4	ƒ 26,908	ƒ 34,167	ƒ 46,086	ƒ 20,641	ƒ 27,346	ƒ 38,336
		s1 -> s2	ƒ 19,925	ƒ 23,231	ƒ 25,764	ƒ 25,933	ƒ 36,007	ƒ 59,968
		s2 -> s3	ƒ 26,735	ƒ 37,619	ƒ 61,817	ƒ 22,311	ƒ 36,413	ƒ 59,309
		s3 -> s4	ƒ 23,191	ƒ 32,152	ƒ 51,445	ƒ 13,877	ƒ 15,626	ƒ 20,097
	Age of	s0 -> s1	-----	-----	-----	-----	-----	-----
	onset	s0 -> s2	ƒ 94,524	ƒ 102,964	ƒ 110,878	ƒ 91,151	ƒ 125,862	ƒ 170,942
	75 yrs	s0 -> s3	ƒ 71,618	ƒ 91,573	ƒ 121,290	ƒ 62,270	ƒ 75,849	ƒ 91,060
		s0 -> s4	ƒ 61,988	ƒ 79,181	ƒ 103,883	ƒ 89,274	ƒ 105,373	ƒ 125,147
		s1 -> s2	ƒ 38,088	ƒ 34,436	ƒ 31,045	ƒ 5,438	ƒ 3,972	ƒ 2,933
		s2 -> s3	ƒ 49,758	ƒ 77,525	ƒ 141,570	ƒ 41,506	ƒ 46,990	ƒ 53,056
		s3 -> s4	ƒ 38,653	ƒ 50,338	ƒ 65,985	-----	-----	-----

Table 14.17 - Approximation by *friction costs technique*; option α

Table 14.17 presents results based on the *friction costs technique*. According to observations presented in section 11.7, the savings in production losses equal 5% of the corresponding savings in the *human capital approach*, as indicated by quotient 14.2.

$$\frac{\text{total direct costs} - 0.05 \times \text{production growth} - \text{disability facilities savings}}{\text{realised sight gain} \quad \text{or} \quad \text{prevented vision loss}} \qquad (14.2)$$

For cohorts where NIDDM develops at the age of 35 or 55 years, all ratios are positive. Pure financial considerations provide insufficient ground for justifying ophthalmic care. For the oldest onset cohorts, table 14.17 presents many vacant positions, following negative medical effects. The other outcomes for these cohorts provide a meagre basis for further analysis because of considerable random disturbances. Therefore, these results are left out of consideration in the next paragraph.

At higher discount rates, most ratios get a higher value, because costs precede effects and benefits in time. The comparison of NIDDM-a and NIDDM-b fails to reveal a clear pattern, but in most cases the NIDDM-a ratio is larger than the NIDDM-b ratio. In block A, scenario two enables to minimise the costs for the age of onset of 35 years at a discount rate of 5%. This scenario offers the lowest average costs in three out of four cases, with the exception of NIDDM-a in block B where it presents the third best alternative. For the age of onset of 55 years and a discount rate of 5%, scenario four offers the best alternative in three cases and the second best alternative in one case. These alternatives are, however, roughly twice as expensive as the minima of the average costs for the youngest age of onset.

The next chapter presents concluding remarks on the results for NIDDM patients.

15

Concluding Remarks

15.1 Introduction

In the previous chapter, the simulation outcomes for NIDDM patients were presented accompanied by explanatory notes about specific elements of the analysis. The present chapter considers the results in a wider perspective. The next three sections relate to the three ages of onset distinguished by the simulation. Each section deals with (1) epidemiologic results, (2) costs, effects and benefits, and (3) cost-effectiveness. Finally, the concluding section discusses some general outcomes.

15.2 Age of Onset 35 Years

At the onset of NIDDM, life expectation decreases by eight to eleven years, or by 20% to 24% (cf. table 14.1, section 14.2). Other investigations revealed a reduction in life expectation by ten to twelve years [STG 91:30]. As we already know, the simulation, as well as the prognosis to be presented in part E, relate to periods that stretch well into the twenty-first century. Consequently, the simulation chooses a slightly more auspicious approach for reasons similar to those presented for IDDM cohorts in section 11.2. In other words, the simulation presumes that outpatient diabetes education, self-management and the treatment of complications will continue to improve in the near future, so that diabetic patients may enjoy a rising life expectation.

Figure 14.1 and figure 14.2 (section 14.3) reveal that the prevalence rates of DR, ME, PDR, visual impairment and blindness correspond to the rates mentioned in table 3.2 (section 3.7) and in table 13.6 (section 13.7). The three grades of DR unquestionably attain higher prevalence rates for insulin taking patients than for not-insulin taking patients. Despite these salient differences, the simulation chooses the same parameters for NIDDM-a and NIDDM-b cohorts to imitate the progression of blindness and visual

impairment. The sections 13.5 and 13.6 discuss this decision. Nonetheless, there exists a positive correlation between the severity of DR and the risk of blindness and visual impairment, other than blindness. A differentiation in the prevalence rates of visual disorders would therefore be justifiable. Moreover, the simulation estimates the prevalence of visual disorders conservatively, even for NIDDM-b. Therefore, it is quite likely that the simulation underestimates the effects of ophthalmic care, particularly for NIDDM-a patients.

The number of ophthalmic examinations is approximately proportionate to the intensity of ophthalmic care. Consequently, eight times (817%) as many ophthalmic examinations are performed in scenario four as in scenario one (cf. table 14.5, section 14.4). The number of fluorescein angiograms grows at a considerably slower speed: four times (431%) as many fluorescein angiograms in scenario four as in scenario one (cf. table 14.6, section 14.4). Even more striking is the progression in the number of laser treatments. In scenario four, there are on average 43% more panretinal and 150% more focal plus grid laser treatments than in scenario one (cf. table 14.7 and table 14.8, section 14.6). This outcome reveals the same tendency as the results for IDDM, although it is slightly less conspicuous in this context. Therefore, preventing blindness and visual impairment requires a strategy which gives ophthalmic examinations top priority. According to suggestions presented in section 12.3, it is worthwhile to investigate whether paramedical staff members, superintended by an ophthalmologist, might perform routine diagnostic tasks so that the supply of ophthalmic care may expand in the short run.

At a discount rate of 5%, the minimum of the direct costs equals *f* 9,553 (NIDDM-b, scenario 2) per year realised sight gain, and *f* 24,332 (NIDDM-b, scenario two) per year prevented vision loss. For NIDDM-a these minima have higher values: *f* 12,913 (scenario two), and *f* 37,433 (scenario three) respectively (cf. table 14.15, section 14.7). If savings in production losses are determined by the *human capital approach*, the balance of costs and benefits is nearly always negative, at least at a discount rate of 5%, so that macro-economic considerations justify ophthalmic care (cf. table 14.16, section 14.7). The estimates based on the *friction costs technique* never reveal a favourable balance of costs and benefits. At a discount rate of 5%, scenario two offers the most auspicious result in all instances, apart from prevented vision loss for NIDDM-a, where scenario three offers the most favourable result (*f* 27,785) (cf. table 14.17, section 14.7).NIDDM:human capital approach NIDDM:friction costs technique

What pattern do these results reveal at a discount rate of 5%? In three out of four instances, scenario two minimises the direct costs as well as the balance of direct costs

and benefits, determined by the *friction costs technique*, per year realised sight gain or prevented vision loss. Various scenarios offer the best alternative, if benefits are measured by the *human capital approach*. As the simulation approaches effects and benefits conservatively, it seems advisable to consider the *friction costs technique* as guiding principle and to opt for scenario two.

This does not imply, however, that scenario two is the best selection for a programme aimed at minimising the balance of direct costs and benefits per year realised sight gain or prevented vision loss. Practice reveals that a considerable number of NIDDM patients fail to comply with the recommended guidelines for ophthalmic examinations. According to findings in the American state Wisconsin, this applies to 56% of the NIDDM-a patients and to 62% of the NIDDM-b patients [Witkin 84, Dasbach 91]. Epidemiologic evidence suggests that the Netherlands finds itself in a similar set of circumstances [Verhoeven 89:70]. Consequently, it may be advisable to prescribe scenario three in order to realise scenario two among the majority of NIDDM patients. Moreover, the simulation disregards aspects of blindness and visual impairment which are not quantifiable. Precisely, these aspects may be even more decisive in a situation where the foregoing results would create uncertainty as to the choice between scenario two and scenario three for instance.

15.3 Age of Onset 55 Years

Life expectation decreases by four to six years, or by 18% to 22%, at the onset of NIDDM (cf. table 14.1, section 14.2). Other investigations revealed a reduction in life expectation by five to seven years [STG 91:30]. Following previous observations, these auspicious differences seem legitimate, because these outcomes will be the basis of the prognosis in part E which extends to the near future. Then, differences in life expectation between diabetic patients and the general population are likely to decrease to a smaller extent.

According to figure 14.3 and figure 14.4 (section 14.3), the prevalence rates of retinal and visual disorders correspond to the rates indicated in table 3.2 (section 3.7) and table 13.6 (section 13.7). When cohorts reach the retiring age of 65 years, the prevalence rates of visual impairment and blindness approximate to 5% and 1% respectively. Because visual disorders occur at a substantially larger scale after retirement, they cause comparatively small losses in production.

The progression in the number of ophthalmic examinations and fluorescein angiograms resembles closely the development in the youngest onset NIDDM cohorts (cf. table 14.5 and table 14.6, section 14.4). However, panretinal laser treatments reveal a quite divergent progression, because their number increases by 71% to 113% from scenario one to scenario four (cf. table 14.7, section 14.4). The same observation applies to focal plus grid laser treatments, as their volume rises by 209% to 244% (cf. table 14.8, section 14.4). How can this be explained?

A closer analysis of the results for the youngest onset NIDDM cohorts reveals the following. In various scenarios, the number of laser treatments is initially proportionate to the intensity of ophthalmic care. This implies for instance that scenario four counts approximately eight times as many laser treatments as scenario one. Apparently, more frequent ophthalmic examinations discover far more patients for whom laser treatment is indicated. In subsequent years, these differences diminish. Ultimately in scenario four, the number of laser treatments exceeds that number in scenario one by 43% (panretinal; unweighted average of 39%, 42%, 41% and 48%) and by 150% (focal plus grid; unweighted average of 152%, 165%, 132% and 152%) rather than by 700% (cf. table 14.7 and table 14.8, section 14.4). After relatively large numbers of laser treatments during earlier years in scenario four, the need for further laser treatment decreases automatically in subsequent years, because these treatments are supposed to have lasting effects. In scenario one the number of laser treatments is initially much smaller, so that a larger need remains during for later years, say twenty to forty years after the start of the simulation. This *"catching up"* demand may only be achieved, in so far as patients are still alive. In cohorts where NIDDM develops at the age of 55 years, mortality impedes this catching up.

At a discount rate of 5%, the average direct costs manifest considerable spread. According to table 14.15 (section 14.7), the minima of the direct costs per year vision gain fluctuate from *f* 12,876 (NIDDM-a, scenario 1, realised sight gain) to *f* 40,655 (NIDDM-a, scenario 2, prevented vision loss). At the same discount rate, the balance of costs and benefits, determined by the *human capital approach*, is occasionally negative for NIDDM-a and in all instances positive for NIDDM-b (cf. table 14.16, section 14.7). In other words, pure financial considerations suffice to justify ophthalmic care for insulin taking patients. In all instances, scenario two enables to reach the minimum, which varies between *–f* 1,431 and *f* 1,644. The *friction costs technique* obviously leads to less favourable outcomes (cf. table 14.17, section 14.7). At a discount rate of 5%, the minima of the costs minus benefits per year vision gain fluctuate from *f* 11,342 to *f* 33,465 (twice in scenario four, once in scenario one and scenario two).

In short, the balance of costs and benefits is far less favourable for cohorts where NIDDM develops at the age of 55 years than for younger onset cohorts, including IDDM patients. Moreover, the results present insufficient support to select a particular scenario. It is worth observing however that the relative number of years of prevented blindness is not much less than in cohorts where NIDDM develops at the age of 35 years (table 14.3, section 14.3). Consequently, the less favourable balance of costs and benefits may be explained by the fact, that most blindness and visual impairment occur after patients reach the retiring age.

15.4 Age of Onset 75 Years

According to table 14.1 (section 14.2), these patients' life expectation decreases by one to two years at the onset of NIDDM. A publication by the *Steering Committee on Future Health Scenarios* presents statistics on the decrease in life expectation for ages of onset varying from 15 to 70 years [STG 91:30]. The trend which emerges from these statistics may be extrapolated to the age of onset of 75 years. It confirms the outcomes of the simulation taking into account previous observations on the expected course of the relative life expectation for diabetic patients.

The progression of retinal and visual disorders, represented by figure 14.5 and figure 14.6 (section 14.3), harmonises with the rates mentioned in table 3.2 (section 3.7) and table 13.6 (section 13.7). As the life expectation of these patients equals some seven to nine years at the onset of NIDDM, the disorders cannot reach their maximum prevalence rates, with the exception of DR. For this reason, ophthalmic care prevents far less blindness caused by DR than in younger onset cohorts (cf. table 14.3, section 14.3). According to the discussion in section 14.3, most blindness in these cohorts results from the rapid progression of DR in a limited number of eyes. This hampers the effectiveness of ophthalmic care in the oldest onset cohorts.

After the observations in the previous section, it is understandable why the number of fluorescein angiograms[1] and laser treatments grows relatively faster in these cohorts than in younger onset cohorts, when the intensity of ophthalmic care rises (cf. table

1 In diagnosing elderly patients, ophthalmologists tend to apply fluorescein angiography with some reticence (verbal communication by prof.dr. F. Hendrikse, Professor of Ophthalmology, Department of Ophthalmology, University of Limburg School of Medicine, Maastricht). The simulation disregards this refinement. Consequently, the direct costs presented in the previous chapter may overestimate the actual direct costs for the oldest onset cohorts.

14.6, 14.7 and 14.8, section 14.4). Obviously, this is detrimental to the balance of costs and benefits, as the tables 14.15, 14.16 and 14.17 in section 14.7 confirm. In so far as ophthalmic care succeeds in preventing blindness or realising sight gain, the average costs are considerably higher than for patients who develop NIDDM at a younger age. A similar unfortunate course of events appears after balancing costs and benefits, regardless of whether the calculations are based on the *human capital approach* or the *friction costs technique*. Consequently, this investigation cannot present arguments for providing the oldest onset NIDDM patients more intensive ophthalmic care than other patients in the same age group.

15.5 Conclusion of the Chapter

Following cost-effectiveness calculations based on the *friction costs technique*, financial considerations fail to provide sufficient arguments to justify special ophthalmic care for NIDDM patients. This statement is based upon an simulation starting from numerous conservative assumptions. At a discount rate of 5%, the costs per year vision gain equal at least *f* 9,553 for not-insulin taking patients and *f* 12,913 for insulin taking patients who develop NIDDM at the age of 35 years.

Epidemiologic findings suggest however that the incidence of NIDDM is concentrated among older onset patients [Palumbo 76; Melton 83a; Klein 84a; Krolewski 87]. Therefore, the results for the younger onset cohorts may seem less important. Recent research has revealed however that the onset of NIDDM is likely to occur some nine to twelve years before clinical diagnosis [Harris 92]. An investigation by Diglas and associates confirmed these findings indirectly [92]. They found that 23.1 years elapse on average between the diagnosis of IDDM and the first laser treatment, whereas this time difference equals 15.9 years for NIDDM. At each moment after the onset of DM however, the prevalence of PDR is evidently higher for IDDM than for NIDDM, whereas the prevalence of ME is at most marginally higher for NIDDM than for IDDM (cf. figures 11.3 and 11.4, section 11.3; figures 14.1 and 14.2, section 14.3). Therefore, it may seem obvious that laser treatments are performed earlier after the onset of IDDM than of NIDDM. In practice however, the opposite is true. This may point to the delayed diagnosis of NIDDM, which gives the results for the age of onset of 35 years more weight. Mutatis mutandis, this also applies to the results for cohorts where NIDDM develops at the age of 55 years, albeit to a lesser extent.

E

Prognosis

16

Starting Points

16.1 Introduction

The results presented in previous chapters concern cohorts with an initial size of 10,000 female or 10,000 male diabetic patients. These numbers do not regard the actual incidence of IDDM or NIDDM in a specific country. They are primarily connected with the simulation technique, because Monte Carlo applications only yield dependable outcomes for larger cohorts. So far, the outcomes of this investigation have provided assistance in answering the central research questions, presented in chapter five, from a rather general perspective. The foregoing chapters indicate, for instance, how much blindness caused by DR may be prevented in various scenarios of ophthalmic care at incidence and prevalence rates which are likely to prevail in various parts of Western Europe and Northern America. They also enable one to gain insight into the cost-effectiveness of ophthalmic care in countries where ophthalmic care charges, prices and productivity levels are comparable to those of the Netherlands in 1992. Additionally, the results can promote answers to more specific problems, because basic arithmetic operations can convert the outcomes to cohorts of any size. Along these lines, the present part of this study tries to answer the two following questions.

> *How much vision loss caused by retinopathy among diabetic patients can present-day ophthalmic technology prevent in the Netherlands until the year 2020?*
>
> *What resources does this care demand with respect to personnel, matériel and finances?*

Besides outcomes of the simulation, the prognosis needs information on the prospective age composition of the general population and on future incidence rates of IDDM and NIDDM. This chapter indicates the sources of this information. It also indicates

which data the prognosis borrows from the simulation, what hiates appear and how the prognosis fills these gaps. Then, chapter 17 focuses on methods, whereas chapter 18 presents the principal outcomes of the prognosis, followed by concluding remarks in chapter 19.

16.2 Population Forecasts

The prognosis follows the general population in the Netherlands from 1900 to 2020. It yields annual statistics on the composition of the population, where the first of January is the datum date. Going back as far as 1900 would be unnecessary, if there existed reliable data on the prevalence of DM with adequate differentiation by gender, age, type of DM and medication kind. Such statistics are not available however [STG 91:4-5, 29]. To fill this gap up, the prognosis relates the incidence rates of DM from the start of the century to the composition of the general population. This ascertains that all patients suffering from IDDM or NIDDM in the year 1993 are followed from the onset of DM. In the previous century, IDDM patients had a life expectation of one to two years at the onset of DM. Patients who developed NIDDM in the nineteenth century were in 1900 at least 30 years old. According to life tables for the general population, all these patients must have died before 1993 [CBS 71, 73, 88b, 91a]. The next chapter presents further details on the technique used by the prognosis for calculating the prevalence of DM.

The size and composition of the general population in the Netherlands before 1993 are directly based on CBS census findings which are differentiated by gender. The statistics used by the prognosis distinguish three age groups for 1900 to 1959, thirteen age groups for 1960 to 1967, fifteen age groups for 1968 to 1976, sixteen age groups for 1977 to 1983 and eighteen age groups for 1984 to 1986 [CBS 60..92, 84]. The findings for 1987 to 1992 specify 95 ages and one age group (≥95) [CBS 87, 88a, 89a, 90, 91c, 92d]. Starting from these sources, the prognosis model estimates the population composition by gender and by age for the years 1900 to 1986 by approximation techniques that section 17.2 will introduce.

As to the years 1993 to 2020, the size and composition of the general population in the Netherlands are determined annually (datum date: January 1st) on the basis of the three variants in the *Population Forecasts*: low, medium and high [CBS 89b, 91b, 92c]. These sources present predictions for the years 1995, 2000, 2005, 2010, 2015 and 2020. For the remaining years of the period 1993-2020, the expected size and composition of the population are calculated by linear interpolation for reasons to be dis-

cussed in section 17.2. The estimates for 1993 and 1994 are derived from the census statistics of 1992 and the forecasts of 1995. For each year, the prognosis distinguishes 90 ages plus one age group (≥90) per gender.

The prognosis computes the expected prevalence of DM for each of the three variants in the *Population Forecasts* separately. May the low and the high variant be considered as the lower and upper limits of a statistical confidence interval that embraces deviations from the medium variant not larger than the standard deviation? In the low variant, each demographic factor - natality, mortality, foreign emigration or immigration - has an expected value at the limit of a 68% confidence interval such as to minimise population growth. Consequently, this variant uses the lowest natality and immigration rates as well as the highest mortality and emigration rates. However, it is quite unlikely, that all deviations from the medium variant are simultaneously oriented towards low population growth. The opposite reasoning applies to the high variant. In other words, the low and the high variant are based on a quite improbable set of presumptions. Therefore, the actual 68% confidence interval of the *Population Forecasts* is situated well within the interval delimited by the low and the high variant [Beer 91, 92b].

For each demographic factor, the *Population Forecasts 1988-2050* uses a specific limit year. Before that year, the demographic factor progresses according to estimates. Thereafter, it remains constant. Beyond the limit year, the outcomes are forward calculations rather than forecasts. For foreign migration, the limit year is 2000 and for mortality 2010. Regarding natality, the limit cohort dates back to 1975. This implies that the prognosis estimates fertility rates only for women born in 1975 or earlier. Each age has its own limit year. For younger age groups, the forecasts are less certain than for older age groups [Beer 92a]. Consequently, predictions for NIDDM may be more accurate than for IDDM.

16.3 Incidence of IDDM and NIDDM

Several sources present findings on the incidence of DM [Palumbo 76; Melton 83a; Stewart-Brown 83; Beaufort 88; Bingley 89; Dahlquist 89; Joner 89; Keiding 89; Rewers 89; Wagenknecht 89; Bruno 90; Haffner 90, 91]. Most of these studies relate to European countries - Denmark, Finland, France, Italy, Luxembourg, Netherlands, Norway, Poland, Sweden, United Kingdom - or to the United States. Some investigations are confined to a particular ethnic group, to children or to a specific region. Incidence rates may differ considerably within rather small geographical distances. For instance, Beaufort and associates point out that the relative incidence of IDDM before

the age of fifteen years is nearly three times as high in the Netherlands as in France [88]. Ethnic differences may also be significant. In the American state Alabama, the incidence of IDDM before the age of twenty years was almost five times greater for White than for Black boys and one and a half times greater for White than for Black girls [Wagenknecht 89]. According to two American studies in San Antonio (Texas) and San Luis Valley (Colorado), prevalence rates of NIDDM were significantly higher for Hispanic than for Anglo persons: more than twice as high for men and almost five times as high for women [Hamman 89a; Haffner 91]. Obviously, these studies do not lead to uniform findings. It would be incorrect to apply the averages of these statistics to the Netherlands, because there is no ground for assuming that the incidence or prevalence of DM in the Netherlands equals the average of the results under consideration.

Considering the weight of geographic and ethnic factors, it seems necessary to select epidemiologic data that relate directly to the Netherlands. Besides statistics on the incidence of IDDM among children [Vaandrager 84], there are findings from a national network of measuring-stations for *Continuous Morbidity Registration* [STG 91:27]. They distinguish ten age groups per gender, but they fail to specify IDDM and NIDDM. Table 16.1 presents these statistics plus results from well-known American studies for the sake of comparison.

[STG 91:27]			[Allen 86]			[CCEU 85]			[M ølton 83b]		
Age	F	M	Age	F	M	Age	F	M	Age	F	M
0-4	0.6	0.7	0-4	0.8	1.0						
5-9	1.0	1.2	5-9	1.7	1.7				0-9	0.8	0.5
10-14	1.5	1.4	10-14	2.3	3.3						
15-19	0.9	1.2	15-19	0.9	1.7				10-19	1.8	1.4
20-24	1.6	1.4	20-24	0.8	1.0	<25	2.9*	----	20-29	1.8	1.7
25-34	2.7	3.3	25-29	0.8	1.4						
35-44	6.5	7.0				25-44	15.3	23.3	30-39	5.2	4.1
45-54	18.7	20.8				45-54	72.4	18.9*	40-49	11.1	10.0
55-64	26.1	26.1				55-64	95.5	33.2*	50-59	15.9	40.6
≥65	52.7	49.9				≥65	94.1	85.9	60-69	46.4	63.5
									70-79	53.5	74.1
									≥80	68.1	99.4
* Figure does not meet standards of reliability or precision.											

Table 16.1 - Yearly incidence of DM per 10,000 female or male inhabitants

The investigation by Allen and associates [86] concerns the incidence of IDDM in the American state Wisconsin, where Klein and co-workers made several studies of DR.

Until the age of nineteen years, the incidence is greater in Wisconsin than in the Netherlands. Thereafter, the opposite is true. A review by the *Carter Center of Emory University* presents unpublished data from the *National Health Interview 1978* [CCEU 85]. The unweighted average of the eight rates for the ages of twenty-five years and older is 136% higher than the corresponding data for the Netherlands. From evidence mentioned in this review as well as from other sources [ADA 91], one might infer that for every person diagnosed as having diabetes in the United States, there may be another who has diabetes but remains undiagnosed. Melton and co-workers [83b] studied the yearly incidence of DM between 1960 and 1969 in Rochester (Minnesota), a city with more than 50,000 inhabitants. The unweighted average of all the incidence rates in this investigation is 146% larger than the corresponding average for the Netherlands.

Do the findings in the United States confirm the data for the Netherlands? As a rule, the incidence rates of DM are positively correlated to the degree of geographical latitude. This has already been illustrated by the observation that the incidence rates in France are considerably lower than those in the Netherlands, which faces more favourable perspectives than Scandinavian countries. Regarding climatic conditions, the American states Minnesota and Wisconsin may be compared to Finland and Sweden. Therefore, the findings in these states are compatible with the statistics for the Netherlands. The national data for the United States, published by the CCEU [85], can hardly be compared to those of the Netherlands, because the United States offers far greater climatic and ethnic disparities. However, the remark by the CCEU on the large number of undiagnosed NIDDM patients may also apply to the Netherlands [STG 91:2].

The previously mentioned incidence rates for the Netherlands do not distinguish between IDDM and NIDDM. This causes no problems however. Following the distinction borrowed in section 2.3 from Klein and co-workers [84b], the prognosis assumes that patients who develop DM before the age of thirty years suffer from IDDM, and otherwise from NIDDM. This enables one to relate the incidence rates in table 16.1 unambiguously to IDDM and NIDDM. Section 17.3 will explain how the prognosis transforms the rates per age group into rates per age.

[Klein 84c] Wisconsin United States		[Verhoeven 89:69] Heerde, Gelderland the Netherlands		[Reenders 92:58] Hoogeveen, Drenthe the Netherlands	
Duration of NIDDM (yr) (N = 1370)	Insulin treatment	Average duration of NIDDM (yr) (N = 137)	Insulin treatment	Average duration of NIDDM (yr) (N = 387)	Insulin treatment
0-4	26.5%	7.5	21.9%	8.1	16%
5-14	43.5%				
≥ 15	71.5%				

Table 16.2 - Frequency of insulin taking by duration of NIDDM

Finally, NIDDM patients are classified by medication type in the categories NIDDM-a and NIDDM-b. Because table 16.1 does not support this distinction, the prognosis uses the findings presented in table 16.2. The relative number of insulin taking NIDDM patients is considerably larger in Wisconsin than in Heerde or Hoogeveen. According to the investigation by Klein and associates, the proportion of insulin taking patients increases as the duration of NIDDM rises. Although no evidence was found on this issue in the Netherlands, the prognosis may not ignore the findings by Klein and co-workers.[1]

$$P(\text{NIDDM-a} \mid \text{NIDDM}) = \frac{m}{1 + e^{b(t-h)}} \quad \{b,h,m,t \in \mathbf{R} \mid b<0;h>0;0\leq m\leq 1\} \quad (16.1)$$

Respecting the study results by Klein et al., Reenders and Verhoeven, the prognosis approximates the relative number of insulin taking NIDDM patients by an S-curve formally presented in equation 16.1. The likelihood of NIDDM-a among NIDDM patients depends on the variable t, which represents the duration of NIDDM. In the prognosis, the three parameters have the following values: b –0.25; h 10; m 0.5. Figure 16.1 presents this relationship graphically. Following the investigations by Reenders and Verhoeven, some 19% of all patients take insulin eight years after NIDDM is diagnosed. The increasing path of the curve corresponds to the results found by Klein and co-workers.

1 In the Netherlands, there exists a positive correlation between the duration of NIDDM and the proportion of insulin taking patients, according to verbal and written information by dr. E. van Ballegooie (Internist, De Weezenlanden Hospital, Zwolle) and dr. K. Reenders (Associate Professor, Department of General Practice, State University School of Medicine, Groningen). The parameters presented in the following section largely depend on this knowledge. Herewith, I acknowledge my gratitude for this essential information.

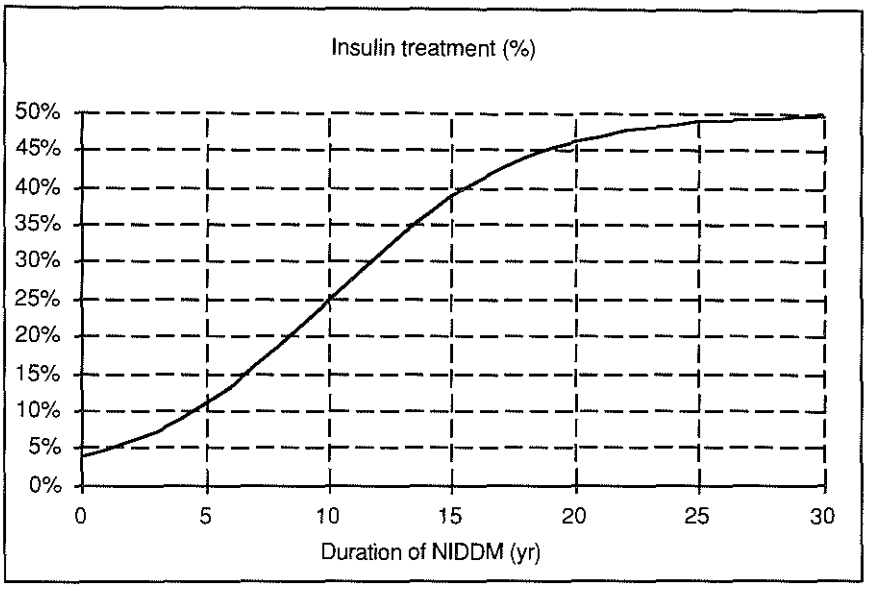

Figure 16.1 - Presumed relation between duration of NIDDM and insulin treatment

This curve invites a marginal note. Oral treatment enabled effective metabolic control for 73.3% of the NIDDM patients who were diagnosed less than six years ago, and for 60.7% if the diagnosis was less than nine years old [Lebovitz 83; Gerich 89]. This implies that the curve should shift upwards to reach 26.7% after six years and 39.3% after nine years. However, according to estimates based on findings in Wisconsin [Klein 84h], some 30% of the American NIDDM patients take insulin [Galloway 90]. This publication does not specify the average duration of NIDDM among these patients. Table 19.2 in section 19.3 will reveal that the average duration of NIDDM since diagnosis equals more than 9.5 years for the Netherlands in 1993. If this outcome approximates the actual average duration in the United States, the curve in figure 16.1 closely reflects the actual progression. Apart from this, the proportion of insulin taking patients in France was only 8.8% among 1,093 NIDDM patients who were diagnosed more than ten years earlier on average [Papoz 88].

16.4 Frequency of Eye Disorders, Tests and Treatments

The simulation, of which part C and part D presented the principal outcomes, calculates for each cohort results such as the prevalence of retinal and vision disorders as well as the frequency of ophthalmic tests and treatments. These results are classified by gender and by duration of IDDM, NIDDM-a or NIDDM-b, where necessary sub-

divided by age of onset. The integral presentation of the simulation output would require far too much space, even in an appendix. From these results, one might for instance deduce directly how many panretinal laser treatments are performed during the thirtieth year after the onset of IDDM in a cohort which initially counts 10,000 female patients and where ophthalmic care follows the guidelines of scenario two. Analogously, the results help to answer the question how many persons are blind as a result of DR twenty years after the onset of NIDDM-a at the age of 55 years in the cohort initially holding 10,000 male patients who receive no ophthalmic care. The outcomes also indicate yearly for each cohort how many patients are still alive. Thus, the average prevalence of eye disorders, tests and treatments per patient is found after dividing the total absolute yearly prevalence by the number of survivors. Then, the prognosis model multiplies the average prevalence and the number of diabetic patients per age and per gender. The latter number equals the product of the forecasted number of inhabitants of a particular age and gender and of an age and gender specific incidence rate. The total prevalence is the sum of all the prevalence results per age and per gender. The next chapter presents further details on this calculation.

These prevalence statistics do not suffice for the prognosis, because they only concern patients who receive ophthalmic care in the scenarios one to four as soon as they develop DM. According to Verhoeven's findings however, 50% of the NIDDM patients had an ophthalmic examination less than once in the foregoing three years [89:70]. Investigations in other countries reveal similar results for IDDM and NIDDM patients [Witkin 84; Day 87; Dasbach 91]. The prognosis may not ignore these outcomes, not the least because conclusive evidence on the effectiveness of laser treatment was found rather recently [DRSRG 81; ETDRSRG 85]. It goes without saying, that care providers as well as patient organisations, like the *Dutch Diabetes Association*, started large-scale education campaigns to highlight the importance of frequent ophthalmic examinations only in subsequent years. Thereafter, a few years had to pass before these campaigns became effective. Moreover, many Dutch hospitals used to have no ophthalmic laser equipment. The diffusion of argon lasers was <10% in 1980, <30% in 1985 (graph reading) and 68.4% in 1992 [Vondeling 93]. This study reveals for March 1992 that 109 out of the 111 retinal lasers in Dutch ophthalmic clinics were argon lasers. Recent issues of magazines for diabetic patients - *Bloedsuiker<10* and *DIABC* - stress the danger of DR and the importance of ophthalmic examinations. Obviously, all care providers - diabetes nurses, general practitioners, internists, ophthalmologists - emphasise the importance of frequent ophthalmic examinations.

As a result of diabetes education and increases in ophthalmic capacity, the number of laser treatments grew considerably in recent years, not the least because ophthalmic

clinics without laser equipment referred many patients to other ophthalmic clinics. So far however, no findings have been published on this subject for the Netherlands. Continuing the previously mentioned conservative course, the prognosis assumes that a new policy on ophthalmic care is not effective until 1993, so that no diabetic patient received ophthalmic care before that year. Although this pessimistic starting point leads to less favourable results, it may seem justifiable, because laser treatments were not performed at large scale until recently. This assumption prohibits applying the previously discussed simulation results to IDDM and NIDDM patients who were diagnosed before 1993. As opposed to the patients in the simulation, they had to face a time-lag between the diagnosis of DM and the moment when they started to benefit from ophthalmic care.

	Age of onset	Time-lag between onset of DM and start of ophthalmic care (yr)			
		0	10	20	30
IDDM	15	10	8	8	8
NIDDM-a or NIDDM-b	35	20	16	16	0
NIDDM-a or NIDDM-b	55	20	16	0	0
NIDDM-a or NIDDM-b	75	20	0	0	0

Table 16.3 - Number of cohort simulations

In order to solve this problem, the simulation model was applied to situations where patients do not receive ophthalmic care until some years after the diagnosis of DM. The last three columns of table 16.3 present a survey. The preceding column indicates cohort simulations where patients receive ophthalmic care without delay after the onset of DM. The results in part C and part D relate to these seventy cohort simulations for both genders, five scenarios, four ages of incidence and two types of medication for NIDDM patients. Obviously, the last three columns in table 16.3 neglect scenario zero. The survey reveals that the additional cohort simulations for IDDM patients relate to a time-lag of ten, twenty or thirty years. Before this time-lag has elapsed, patients are fully deprived of ophthalmic care. Thereafter, they follow one of the scenarios one to four. For the age of onset of 35 years, the additional simulations regard a delay of ten and twenty years; only the delay of ten years is examined for patients who develop NIDDM at the age of 55 years. No additional simulations are performed for the oldest onset groups. The total number of additional cohort simulations equals seventy-two as indicated in the last three columns of table 16.3.

Table 16.3 raises two questions. Why are the additional simulations confined to time-lags equalling multiples of ten years? And why are no simulations performed for larger

time-lags than those mentioned in table 16.3? Both questions have a practical answer. As section 7.6 observed, ten cohorts of 10,000 IDDM patients require almost one week computer processing time. This may answer the first question. Furthermore for each age of onset, the outcomes of the additional simulations reveal that ophthalmic care is hardly effective in the simulations with the largest time-lag mentioned in table 16.3. In other words, these results approximate those of scenario zero. Therefore, it would be meaningless to analyse longer time-lags. The next chapter explains how the prognosis determines the results for time-lags and ages of onset omitted in table 16.3.

17

Methods

17.1 Introduction

The prognosis model processes the empirical findings considered in the previous chapter by methods which will be presented in the present chapter. The next sections successively analyse the calculation of (a) the population size, (b) the incidence rates, (c) the hazard rates, (d) the distribution of NIDDM patients by medication and (e) the prevalence rates of eye disorders, ophthalmic examinations and treatments.

17.2 Population Size

The prognosis requires annually - datum date: January first - a specification of the composition of the general population by gender and by age, the latter expressed in years. The available statistics offer this degree of specificity only for 1987-1992, so that approximations are necessary in other years. For the period 1900-1959, the data distinguish three age categories (0-19, 20-64, ≥65 years) as well as the proportion of men in the total population. On the basis of this proportion, the age groups are divided by gender. Consequently, six categories emerge which are distributed by age following equation 17.1.

$$\alpha_{a,b..e} = \frac{\prod_{t=b}^{a} (1 - \lambda_{t+0.5})}{\sum_{m=b}^{e} \prod_{t=b}^{m} (1 - \lambda_{t+0.5})} \quad \{a,b,e,m,t \in \mathbf{Z};\ \alpha,\lambda \in \mathbf{R} \mid b \le a \le e;\ 0 \le \lambda \le 1\} \quad (17.1)$$

The symbols $\alpha_{a,b..e}$ represent the ratio of the number of persons who are *a* years old and the number of persons with the ages of *b* to *e* years. After the previous sub-

division, α concerns either men or women. The hazard rates $\lambda_{t+0.5}$ are derived from the Dutch mortality rates for 1946-1950, 1951-1955 or 1956-1960 [CBS 71][1]. To the subscript of λ, *0.5* is added, because all persons of the age of t years are on average $t + 0.5$ years old.

This approximation invites at least three marginal notes. First, from 1900 to 1946, life expectation increases by 18.4 years for men and by 18.1 years for women [CBS 84:30]. As a result, hazard rates change considerably. Second, the ratio of men is different in the three age categories, although the statistics mention only one ratio for the total population. Third, the approximation method assumes that the population remains constant regarding size and composition by age and gender. However, the number of inhabitants in the Netherlands increases between 1900 and 1946 by 82.3% from over five million to more than nine million.

Can the approximation method be justified despite these critical notes? Each observation is analysed separately to answer this question. The increase in life expectation, which is the issue of the first note, mainly results from a reduction in childhood mortality. Between 1900 and 1946, the life expectation for men increases by 36.1% at birth, by 21.6% at the age of one year and by 16.9% or less at the ages of ten, twenty, thirty and forty years. For women, the rise equals 33.9% at birth, 21.7% at the age of one year and 16.2% or less at the other four ages [CBS 84:30]. Consequently, the hazard rates after childhood change far less dramatically than the spectacular rise in life expectation at birth might suggest. By using the actual hazard rates, the population composition by age within each of the three age categories would only change moderately. Moreover, the centre of gravity of these mutations is situated in the first half of the period 1900-1946.

Age (yr)	Proportion of all females	Proportion of all males	Overrating of number of females
0 - 19	28.00%	28.78%	1.37%
20 - 64	56.27%	56.67%	0.35%
≥ 65	15.73%	14.55%	-3.89%

Table 17.1 - Distribution over 3 age categories based on hazard rates 1946-1950 [CBS 71]

1 This publication presents twenty hazard rates per gender for each of the three periods. On that basis, 111 hazard rates were calculated per gender for the ages of 0.0, 0.5, 1.5, ... 109.5 years. This calculation is an approximation starting from 2×96 crude mortality rates for 1972 and from 2×111 crude mortality rates for 1983-1987 [CBS 73, 88b]. The hazard rates for 1946-1950 were applied to the period 1900-1950.

Table 17.1 illustrates the second observation. If the population were stationary at the mortality rates for 1946-1950, 15.73% of the women would be 65 years or older, whereas 14.55% of the men would belong to that age group. In the two younger age categories, there are relatively more men than women, although the percentages differ less than in the oldest age group. Mortality rates for earlier periods in the twentieth century would lead to a similar pattern, because women tend to have a longer life expectation than men. At the start of the century however, this discrepancy is smaller than in later years. The statistics for 1900-1959 neglect this evolution, so that the prognosis overestimates the number of women younger than 65 years and underestimates the number of elderly women. The opposite applies to men. The percentages in the last column of table 17.1 refer to the total number of women in all age groups. They indicate to what extent the estimated number of women overrates the actual number.

$$N^{F}_{0..19} = (1 - m)\ (1 - 0.0137)\ N_{0..19} \qquad \{N \in \mathbf{Z}; m \in \mathbf{R} \mid m,N \geq 0\} \qquad (17.2)$$

$$N^{M}_{0..19} = m\ (1 + 0.0137)\ N_{0..19} \qquad \{N \in \mathbf{Z}; m \in \mathbf{R} \mid m,N \geq 0\} \qquad (17.3)$$

For the period 1900-1950, the prognosis model corrects the population composition by the percentages taken from the last column in table 17.1. Equation 17.2 illustrates how the number of women is determined for the age group of zero to nineteen years ($N^{F}_{0..19}$) starting from the proportion of men in the total population (m), the relative overrating of the number of women in this age group (0.0137) and the total number of persons in this age category ($N_{0..19}$). Equation 17.3 presents the calculation for men younger than 20 years ($N^{M}_{0..19}$). For other ages, the prognosis model uses similar equations. The corresponding correction percentages for 1951-1955 and 1956-1959 are based on the mortality rates for 1951-1955 and 1956-1960. The second marginal note does not apply to 1960 and subsequent years, because the available statistics mention the number of men and women in each age group separately.

The third marginal note probably represents the most fundamental critique. The growth in the general population of the Netherlands by 82.3% between 1900 and 1946 excludes stationary progression. The increase mainly results from natural growth, whereas migration is of secondary importance. What repercussions does this have for the approximation method used by the prognosis? At a higher population growth rate, the ratio of any younger to any older age group is *ceteris paribus* larger than in a stationary situation. Consequently, there are not only more persons of the age of zero years as compared to ten-year-old persons, but also more persons of the age of 65 years in proportion to eighty-year-old persons. Within each of the three age categories, the popula-

tion composition in the prognosis differs from the actual composition, because younger ages are under-represented and older ages over-represented. However, the distribution over the three age categories corresponds to the actual distribution, because the available statistics mention the relevant numbers explicitly. The approximation method plus the available statistics may therefore offer reasonable support for the years 1900 to 1959. Moreover, a possible *"noise"* in these statistics affects the outcomes of the prognosis merely marginally. Many patients who develop IDDM or NIDDM before 1960 do not survive until 1993 following decreases in life expectation, like those indicated in the sections 11.2 and 14.2. Consequently, the third marginal note looses much of its weight.

The preceding discussion conveys that differences between the actual population composition and the approximation based on available statistics mainly concern the distribution within the three age categories. This discrepancy decreases, as time advances, because the approximation method uses the mortality rates for the years 1946 to 1950 which obviously fit actual statistics better at the end than at the beginning of the period 1900-1950. Moreover, the prognosis makes provisions to meet the second marginal note. Prior to the presentation of results in the next chapter, it may be observed that the outcomes do not conflict with the results of other studies. Consequently, it seems justifiable to include this approximation method in the prognosis model, although its shortcomings should not be overlooked.

For the years 1960 to 1986, the available statistics distinguish thirteen to eighteen age groups per gender. Each age category is subdivided into age groups of one year by applying equation 17.1 plus actual Dutch mortality rates. Although this calculation also constitutes an approximation, the previous objections are hardly valid. The mortality rates are actual, the statistics are specified by gender, the approximation relates to much narrower age categories and disturbances related to fast population growth are virtually absent. Foreign migration is the principal factor of uncertainty, but its relative size remains rather insignificant in most years up to 1986.

As the statistics for 1987-1992 distinguish ninety-five ages and one age group (≥95) per gender, they do not require further differentiation. For 1993 to 2020, the prognosis borrows data from the *Population Forecasts for the Netherlands 1991-2050* [CBS 89b, 91b, 92c]. The available publications present statistics of three forecast variants - low, medium, high - for the years 1995, 2000, 2005 (medium variant only), 2010 and 2020. Because one of these publications distinguishes ninety ages and one age category (≥90) per gender, no further approximation is needed. To estimate the population composition in intermediate years, several methods were tested, namely (1) linear

interpolation and (2) an cohort simulation based on natality rates, hazard rates, migration rates and the previously mentioned outcomes of the *Population Forecasts*. As the second method comprises all factors that determine the size and composition of the population, it may seem the most appropriate one. However, the available statistics fail to present sufficient details on the size and composition of migration flows. The second method therefore meets the needs of the prognosis to a lower degree than straightforward linear interpolation. The approximations for 1993 and 1994 are based on census data for 1992 and on forecasts for 1995.

17.3 Incidence Rates

From findings on the incidence of DM in the Netherlands, the prognosis model derives the coefficients of four polynomials [STG 91:27]. Two polynomials concern the incidence of IDDM for men and women respectively, whereas the other two polynomials relate to the incidence of NIDDM by gender. In this phase of the computations, the distinction by type of medication for NIDDM patients is not yet relevant. Equation 17.4 formalises the four polynomials. The symbols c_0, c_1, c_2, ... c_n indicate $n + 1$ coefficients, which are determined by a method to be explained forthwith. The variable a is the independent variable, whereas the incidence rate i is the dependent variable. The latter rate equals the yearly number of newly diagnosed IDDM or NIDDM patients per 10,000 men or women in the general population who are a years old.

$$i = c_0 + c_1 a + c_2 a^2 + \cdots + c_n a^n \quad \{a \in \mathbf{Z}; c,i \in \mathbf{R} \mid 0 \leq a \leq 109, 0 \leq i \leq 1\} \quad (17.4)$$

Three techniques were tested for determining the polynomial coefficients: (1) *Vandermonde-matrices*, (2) interpolation and extrapolation by *Lagrange's* formula and (3) multiple linear regression[2]. Regarding the incidence of IDDM, the first two techniques offered an adequate approximation, apart from a few ages near the lower and the upper limit of the age interval (0-29 years). The third technique provoked hardly any inconvenience. Therefore, all the IDDM coefficients in table 17.2 were determined by multiple linear regression. For men and women, polynomials of degree five appear to offer

2 Procedures for the first two methods were borrowed from Press and associates [89:90-3, 104-7]. They were implemented in *Think Pascal 3.0* (Symantec Corporation) for Apple Macintosh computers. For the third method, multiple linear regression modules were used in two spreadsheets (1) *Excel 3.0* (Microsoft Corporation) for Apple Macintosh computers and (2) *Quattro Pro 4.0* (Borland International Inc.) for computers using MS-DOS. The application of different techniques was aimed at the mutual checking of the outcomes.

the best approximation. The coefficient of determination (R^2) and the standard error (σ) point to a persuasive goodness of fit for men (R^2: 0.9999566; σ: 0.0358944). For women, the goodness of fit is only slightly less convincing (R^2: 0.9593259; σ: 4.7171329). Figure 17.1 represents graphically which incidence rates result from the coefficients. These rates closely correspond to the empirical data presented by the STG [91:27].

	Incidence IDDM		Incidence NIDDM	
	Females	Males	Females	Males
c_0	0.404809	0.617153	19.595711	4.385100
c_1	0.056410	-0.012843	-1.413668	-0.345865
c_2	0.021270	0.033611	0.028681	0.007485
c_3	-0.002941	-0.003711	-0.000033	0.000091
c_4	0.000126	0.000140	----	----
c_5	-0.000002	-0.000002	----	----

Table 17.2 - Polynomial coefficients concerning the incidence of IDDM and NIDDM

As to interpolating and extrapolating the incidence of NIDDM, the first two techniques produced coefficients, leading to estimated incidence rates which differ considerably from epidemiological findings for a large number of ages near the lower and upper limit of the relevant age interval (30-109 years). Therefore, the coefficients for NIDDM were determined by multiple linear regression. Polynomials of degree three appear to provide the best fit (men: R^2: 0.9952437; σ: 3.4380153 - women: R^2: 0.9951784; σ: 3.5091546). Table 17.2 presents the coefficients, whereas figure 17.2 pictures which incidence rates result from these coefficients.

According to figure 17.1, the incidence of IDDM has two local maxima at the ages of eleven and twenty-nine years. Immediately after the second maximum, the incidence equals zero following the assumptions of the model. This abrupt drop raises the question, whether figure 17.1 represents the incidence rates of IDDM correctly for the ages of twenty to twenty-nine years. Actually, a fraction of the incidence for these ages may be ascribed to DM type II.

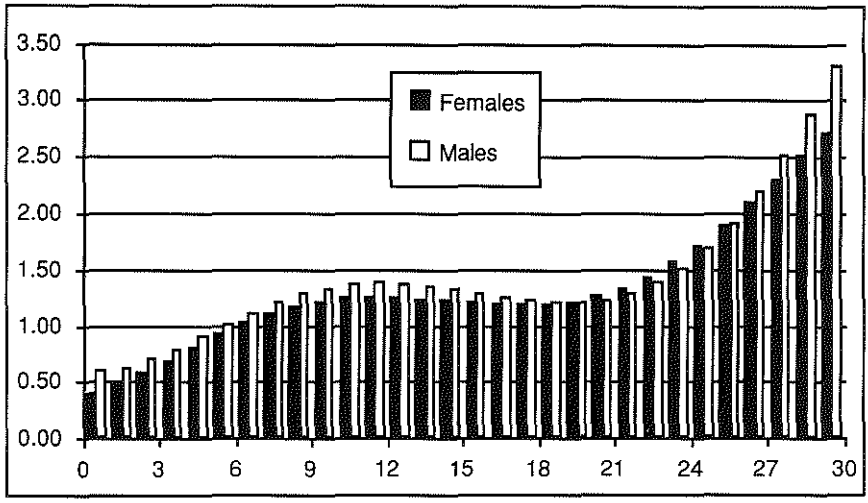

Figure 17.1 - Yearly incidence of IDDM per 10,000 inhabitants by age

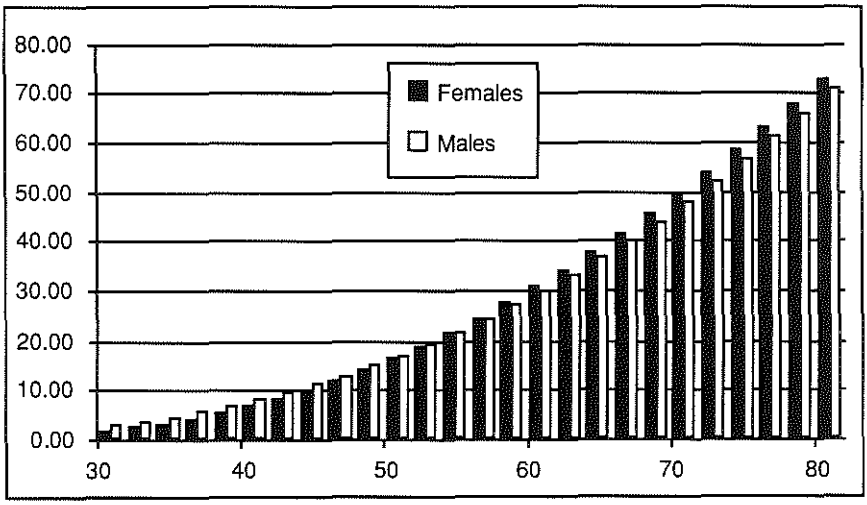

Figure 17.2 - Yearly incidence of NIDDM per 10,000 inhabitants by age

17.4 Hazard Rates

For IDDM patients younger than fifteen years, the prognosis model uses the hazard rates of 1983-1987 for the general population in the Netherlands, which are differentiated by age and gender [CBS 88b]. From the age of fifteen years, the hazard rates of the general population are fine tuned to increases in mortality due to IDDM.

Adjustments are based on the simulation results presented in table 11.1 (section 11.2). From five (IDDM) or ten (NIDDM-a and NIDDM-b) scenarios, the average life expectation is determined by age of onset and by gender. Table 17.3 presents these averages. By the numerical approximation method described in section 8.3, the hazard rates of the general population are adjusted, until they represent a life expectation that deviates less than 10^{-5} years from the life expectation of IDDM patients at their fifteenth anniversary.

	Age of onset	Life expectation at age of onset (yr)	
		Females	Males
IDDM	15	45.80	42.13
NIDDM	35	35.69	31.11
NIDDM	55	21.73	17.49
NIDDM	75	9.22	7.19

Table 17.3 - Average life expectation for IDDM and NIDDM patients based on simulation outcomes (cf. table 11.1 and table 14.1)

The hazard rates for IDDM relate to one age of onset: fifteen years. This simplification has the following rationale. According to the presumptions of the model, the incidence of IDDM is confined to a shorter period than the onset of NIDDM. Moreover, the probability of developing complications by the end of adolescence is relatively small, so that IDDM is unlikely to raise mortality rates significantly before the age of twenty years. Only during the first six months after the onset of IDDM, patients face a considerably higher risk of premature death [Dorman 82, 84; Borch-Johnsen 86]. Therefore, the prognosis model differentiates hazard rates for IDDM by age and by gender but not by age of onset.

Regarding the hazard rates for NIDDM patients, the differentiation by age of onset should not be disregarded. NIDDM may develop at the ages of thirty years or more, following the assumptions of the model. Shortly after the diagnosed onset of NIDDM, rather high frequencies of complications may raise hazard rates considerably [Pirart 78a, 78b; Klein 84c; Dwyer 85; Nathan 86b; Klein 89a; Verhoeven 91; Reenders 92:59]. As to DR, a recent investigation by Klein and co-workers et al. casts some doubt on these findings [92a].

The hazard rates for NIDDM patients are also determined by the numerical approximation method described in section 8.3. From the hazard rates of 1983-1987 for the general population in the Netherlands, three vectors with hazard rates are determined per gender for three ages of onset: 35, 55 and 75 years. The superscripts DM,35, DM,55

and DM,75 in 17.5 refer to the three ages of onset, while the subscripts indicate gender and age. Each vector holds one hazard rate per age starting at 29.5 years. For ages prior to the onset of NIDDM, the vector elements equal the corresponding hazard rates for the general population, indicated by the superscript P. Subsequent hazard rates are modified such as to generate a life expectation at the onset of NIDDM which is equal to the appropriate number in table 17.3.

$$\begin{bmatrix} \lambda^{P}_{F,29.5} \\ \dots \\ \lambda^{P}_{F,33.5} \\ \lambda^{DM,35}_{F,34.5} \\ \dots \\ \lambda^{DM,35}_{F,109.5} \end{bmatrix} \begin{bmatrix} \lambda^{P}_{F,29.5} \\ \dots \\ \lambda^{P}_{F,53.5} \\ \lambda^{DM,55}_{F,54.5} \\ \dots \\ \lambda^{DM,55}_{F,109.5} \end{bmatrix} \begin{bmatrix} \lambda^{P}_{F,29.5} \\ \dots \\ \lambda^{P}_{F,73.5} \\ \lambda^{DM,75}_{F,74.5} \\ \dots \\ \lambda^{DM,75}_{F,109.5} \end{bmatrix} \begin{bmatrix} \lambda^{P}_{M,29.5} \\ \dots \\ \lambda^{P}_{M,33.5} \\ \lambda^{DM,35}_{M,34.5} \\ \dots \\ \lambda^{DM,35}_{M,109.5} \end{bmatrix} \begin{bmatrix} \lambda^{P}_{M,29.5} \\ \dots \\ \lambda^{P}_{M,53.5} \\ \lambda^{DM,55}_{M,54.5} \\ \dots \\ \lambda^{DM,55}_{M,109.5} \end{bmatrix} \begin{bmatrix} \lambda^{P}_{M,29.5} \\ \dots \\ \lambda^{P}_{M,73.5} \\ \lambda^{DM,75}_{M,74.5} \\ \dots \\ \lambda^{DM,75}_{M,109.5} \end{bmatrix} \tag{17.5}$$

After these calculations, there are three hazard rates per age and per gender, like $\lambda^{DM,35}{}_{F,69.5}$, $\lambda^{DM,55}{}_{F,69.5}$ and $\lambda^{P}{}_{F,69.5}$ for 69.5-year-old women. These rates are the starting point for polynomial interpolation and extrapolation by *Lagrange's* formula. By this technique, three coefficients of a polynomial of degree two are determined specified by age and by gender [Press 89:106]. In equation 17.6, which formalises these polynomials, $\lambda^{DM,i}{}_{s,a}$ indicates the hazard rate for patients of gender s and age a who develop NIDDM at the age of i years. After this explanation, it is obvious that the superscripts of the coefficients c_0, c_1 and c_2 refer to gender and age. Provided the age of onset i does not exceed the patient's actual age a, hazard rates may be determined by equation 17.6 for NIDDM patients differentiated by gender, age and age of onset.

$$\lambda^{DM,i}_{s,a} = c^{s,a}_0 + c^{s,a}_1 \, i + c^{s,a}_2 \, i^2 \tag{17.6}$$

$$\{s \in \{F,M\}; a,i \in \{29.5, 30.5, \dots 109.5\}; c, \quad \lambda \in \mathbf{R} \mid i \le a\}$$

In the previous section, polynomial approximation techniques appeared less fitting than multiple linear regression. The use of *Lagrange's* formula may therefore create a surprise. In this context however, only three data points are available. They fail to provide multiple linear regression with an adequate base for estimating the coefficients of a second, or even a first, degree function. These three data points are sufficient for an approximation by polynomials of degree two. Moreover, they happen to generate curves that fit the actual progression of hazard rates after the onset of NIDDM well. Never-

theless, polynomials may lead to unrealistic approximations near the interval limits. Therefore, the prognosis model should not apply such functions, until it is evident that their shortcomings have acceptable proportions[3].

Therefore, the outcomes were submitted to six tests. (1) Are all hazard rates situated in the interval of real numbers (0, 1]? (2) Does life expectation correspond to the relevant value presented in table 17.3 for the ages of onset mentioned in the table? (3) Do women *ceteris paribus* benefit from a longer life expectation than men? (4) Does delaying the onset of NIDDM always increase life expectation? (5) Do younger patients *ceteris paribus* have a longer life expectation than older patients? (6) Is the ratio of the life expectation for the general population and for NIDDM patients acceptable for each age and for each age of onset?

In nearly all instances, these questions receive an affirmative answer. Most exceptions relate to higher ages. Some hazard rates, for instance, are negative or greater than one for ages over 100 years. Therefore, they are *de facto* irrelevant. Exceptionally, life expectation decreases as the onset of NIDDM is postponed. These errors never exceed 0.01 year and always relate to ages over sixty-eight years. The most important disturbances concern patients who develop NIDDM before the age of thirty-five years. Fortunately, these errors are confined to ages below thirty-five years, when NIDDM patients have the same hazard rates as the general population. These disturbances are quite immaterial, because the incidence rates for these ages are limited (cf. figure 17.2 in previous section). Moreover, these errors relate to a small number of years[4] as compared to the total life expectation at the onset of NIDDM. As shortcomings are rather insignificant, it seems justifiable to approximate hazard rates by polynomials of degree two.

17.5 Classification of NIDDM Patients by Medication Type

This classification is based on statistics presented in section 16.3, where an S-curve relates the proportion of insulin taking patients to the duration of NIDDM. It seems superfluous to present further details on this issue.

3 This paragraph may also cast doubt on the application of multiple linear regression in the previous section, because the available set of incidence rates is rather limited. Nevertheless, multiple linear regression offers a more realistic approximation than the two polynomial techniques.

4 If the yearly incidence of NIDDM is constant for the ages of 30 to 35 years, the prognosis model underestimates the hazard rates of these patients for 1,8$\dot{3}$ years.
(1,8$\dot{3}$ = (1 × 4,5 + 2 × 3,5 + 3 × 2,5 + 4 × 1,5 + 5 × 0,5) / 15)

17.6 Frequency of Eye Disorders, Tests and Treatments

The prognosis applies the previously presented approximation techniques to the evidence mentioned in the foregoing chapter. Thus, information appears on (1) the composition of the general population in the Netherlands, (2) the incidence of IDDM and NIDDM, (3) the repartition of NIDDM patients by medication types and (4) the hazard rates of diabetic patients. Starting from this information, thirty cohort simulations are performed for the Cartesian product [Date 81:84] of two types of DM (IDDM, NIDDM), three variants of expected population growth (low, medium, high) and five scenarios of ophthalmic care (s0, s1, s2, s3, s4). From 1900 to 2020, these cohort simulations individually follow all inhabitants who develop IDDM or NIDDM during this period. Annually, they record the progression of retinal and visual disorders due to DR as well as the number of ophthalmic examinations and treatments. By comparing the outcomes in different scenarios of ophthalmic care, it is possible to determine how much blindness and moderate vision may be prevented and which ophthalmic resources are required.

Qua structure, the simulations for the prognosis differ distinctly from the IDDM and NIDDM simulations presented in previous parts of this manuscript. The latter are based on a unique combination of techniques which has not been presented in other publications known to the author. Some of the earlier chapters give insight into this unique combination, not the least for opening up and legitimating the *"black box"* behind these simulations. The prognosis has a far more elementary and straightforward nature. Therefore, an elaborate exposé on its structure would carry things too far. The IDDM and NIDDM simulations analyse closed cohorts with a strictly fixed initial number of patients who are uniform regarding gender, age, age of onset, type of DM and medication type. In the prognosis however, cohorts are open to new IDDM of NIDDM patients. The size of the annual inflow equals the vector product of incidence rates and statistics concerning the composition of the general population in the Netherlands, whereas the yearly outflow comprises deceased patients. Their number corresponds to the vector product of hazard rates and statistics on the composition of the cohort. Therefore, these cohorts count fluctuating numbers of patients who differ qua age, age of onset and medication. These cohorts are dynamic, as opposed to the fixed cohorts which the earlier parts of this manuscript have considered [Kleinbaum 82:64,105].

Migration affects the outcomes of the prognosis indirectly through changes in the size and composition of the general population. Prevalent cases of DM among migrants are disregarded, because the available publications on the *Population Forecasts* present no

statistics on the composition of migration flows by age and gender. However, if these statistics were available, it would hardly be defensible to estimate the prevalence of DM among immigrants, who are at present far more numerous than emigrants, by prevalence rates for the general population in the Netherlands. The fact is that most immigrants come from countries where quite different climatic and nutritional conditions prevail. The use of specific prevalence rates fails to offer a valid alternative, because there exist insufficient statistics on the prevalence of DM in those countries. Moreover, immigrants are of various origins[5]. Consequently, the flow of immigrants should be classified by age, gender and origin. Then, specific prevalence rates should be applied to each class. The *Population Forecasts* do not present these details. Furthermore, many classes may be too small to produce reliable outcomes.

As compared to the IDDM and NIDDM simulations, the prognosis covers far less data elements per patient. It only records the year of birth and the year of onset. As patients die, their cohort positions become vacant for other patients. Therefore, it would be superfluous to record the year of death. It is neither necessary to mention the patient's gender or type of DM, because the prognosis cohorts are specified by gender and type of DM. For NIDDM patients, the distinction by medication type is derived from the year of birth and the year of onset by equation 16.1 (section 16.3). Therefore, a separate data element regarding the medication type would create redundancy. How does the prognosis model determine the frequency of eye disorders, ophthalmic examinations and treatments from these statistics?

$$p^{c}_{s,d,g} = \frac{P^{c}_{s,d,g}}{L^{c}_{s,d,g}} \tag{17.7}$$

$$\{c \in \{0,1,...,4\};\ L, P, p \in \mathbf{R};\ d, g \in \mathbf{Z};\ s \in \{F,M\} \mid 0 \leq g \leq d\}$$

The prognosis model uses the results of the simulations presented in part C and part D (option α). First, let us only consider IDDM. For a specific eye disorder, examination or treatment, the total prevalence $P^{c}_{s,d,g}$ in scenario *c*, for gender *s*, diabetes duration *d* and time-lag *g* of ophthalmic care is divided by the corresponding number of survivors $L^{c}_{s,d,g}$ to find the average prevalence $p^{c}_{s,d,g}$ following equation 17.7. The time-lag *g* of ophthalmic care equals the time-interval between the onset of IDDM and the year when the patient starts to receive ophthalmic care. For reasons presented in section 16.4, the model presumes that diabetic patients do not get ophthalmic care before 1993.

5 Section 19.4 briefly discusses some investigations on the incidence and prevalence of IDDM and NIDDM in Arabic countries.

$$T^{f,c}_{y,s} = \sum_{a=0}^{A} \sum_{i=0}^{\min(a,29)} N^{f}_{y,s,a,i}\ p^{c}_{s,a-i,g} \qquad (17.8a)$$

$$\{T \in \mathbf{R};\ a, i, N \in \mathbf{Z};\ f \in \{H,M,L\};\ y \in \{1993, 1994,...,2020\}\ |\ 0 \le i \le a\}$$

According to equation 17.8a, the previously determined average prevalence is multiplied by the number of diabetic patients $N^{f}_{y,s,a,i}$, which is taken from one of the thirty cohort simulations mentioned at the beginning of this section. For population forecast *f* and year *y* , $N^{f}_{y,s,a,i}$ represents the number of patients with gender *s*, age *a* and age of onset *i*. The difference between *a* and *i* equals *d*, the duration of DM. Equation 17.8a contains a double sum. The first relates to age *a* and ranges from zero to the maximum age A. The second concerns the age of onset *i* and varies from zero to twenty-nine, which is the maximum age of onset of IDDM. As *i* may not exceed *a*, *min(a,29)* - the minimum of *a* and twenty-nine - is the upper limit of *i*. For population prognosis *f* and scenario *c*, the outcome $T^{f,c}_{y,s}$ may represent the total number of patients in year *y* of gender *s*, who face a particular retinal or visual disorder. If equation 17.8a relates to ophthalmic examinations or treatments, $T^{f,c}_{y,s}$ indicates their total number expressed by a real number.

For the sake of simplicity, equation 17.8a assumes that there exists a cohort simulation for every value of *g*. Actually, there is only a limited number of additional simulations as indicated by table 16.3 in section 16.4. This problem is solved in two steps. First, in case of IDDM, one number in the set of integers {0, 1, 2, ..., 30} is allocated to *g* according to 17.8b. Regarding NIDDM, this set is limited to {0, 1, 2, ..., 20}, {0, 1, 2, ..., 10} and {0} for the age of onset of 35, 55 and 75 years respectively.

$$g \begin{cases} \text{if } (a - i + 1993 - y) < 0 \text{ then: } 0 \\ \text{if } (a - i + 1993 - y) > 30 \text{ then: } 30 \\ \text{otherwise: } (a - i + 1993 - y) \end{cases} \qquad (17.8b)$$

$$T^{f,c}_{y,s} = \sum_{a=0}^{A} \sum_{i=0}^{\min(a,29)} N^{f}_{y,s,a,i} \left[\left(1 - \frac{g \bmod 10}{10}\right) p^{c}_{s,a-i,10(g \text{ div } 10)} + \frac{g \bmod 10}{10}\ p^{c}_{s,a-i,10(g \text{ div } 10)+10} \right] \qquad (17.8c)$$

The second step of the solution is based on equation 17.8c, where the number of patients $N^{f}_{y,s,a,i}$ is multiplied by the weighted average of the average prevalence in two simulations with the following time-lags of ophthalmic care: *10(g div 10)* and

10(g div 10)+10. The operator *div* truncates the quotient of g and 10 to an integer. If g is 27 for instance, *10(g div 10)* equals 20. Consequently, statistics are borrowed from two simulations for a time-lag of twenty and thirty years respectively. The operator *mod* is used to determine the weight of these two simulations. It returns the remainder obtained by dividing its two integer operands. If g is 27, *g mod 10* equals 7. Consequently, the first simulation *(g = 20)* has the weight 0.3, whereas the second *(g = 30)* receives the weight 0.7.

This solution lends itself to calculating the prevalence of retinal and visual disorders. However, it is unsuitable to determining the prevalence of ophthalmic examinations and treatments. Let us illustrate this point for treatments by assuming once more that g is 27. Then, the total number of treatments equals 0.3 times the average number of treatments in the simulation for a time-lag of twenty years plus 0.7 times the average number of treatments in the simulation for the thirty-year time-lag. In the latter simulation however, no treatment is performed until thirty years after the start of the simulation. If $a - i < 30$, the calculation for $g = 27$ leads to a number of treatments that is considerably smaller than the normal number in the corresponding scenario. To bypass this difficulty, the first weighing coefficient in equation 17.8c is fixed at one and the second at zero. *Mutatis mutandis*, the same remarks apply to ophthalmic examinations.

$$T^{f,c}_{y,s} = \sum_{a=30}^{A} \sum_{i=30}^{a} N^{f}_{y,s,a,i} \left[\left(1 - \frac{g \bmod 10}{10} \right) p^{c}_{s,a-i,10(g \operatorname{div} 10)} + \frac{g \bmod 10}{10} \, p^{c}_{s,a-i,10(g \operatorname{div} 10)+10} \right] \tag{17.8d}$$

Minor alterations suffice to suit the equations 17.8a and 17.8c to NIDDM. Equation 17.8d illustrates how the sum ranges in equation 17.8c should be modified, so that a and i have a lower limit of thirty years. The upper limit of i equals a, because the age of onset cannot exceed the patient's current age.

17.7 Summary in Schemes

The following schemes present a graphical summary of data processing by the prognosis. Figure 17.3 illustrates the available statistics on the population composition in the Netherlands. For 1900-1992, this information is based on demographic evidence. Where necessary, approximation methods are applied to classify this material by gender and by age. As a result, the prognosis model annually has the disposal of 220

numbers that specify the population composition by gender and by 110 ages. From the *Population Forecasts for the Netherlands 1988-2050* [CBS 89b, 91b, 92c], the model borrows statistics that provide equally detailed information after applying approximation techniques. Figure 17.3 distinguishes three prognosis variants: low, medium and high.

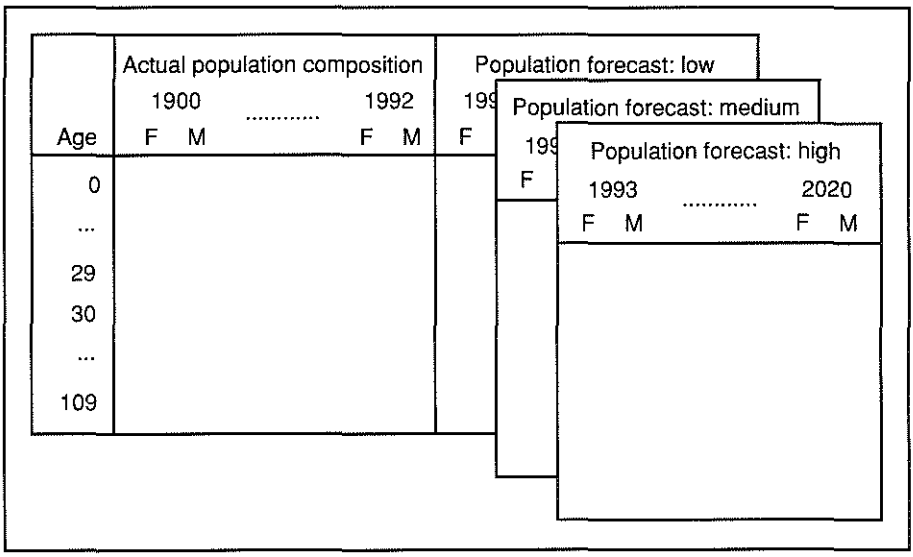

Figure 17.3 - Available statistics on the population composition in the Netherlands

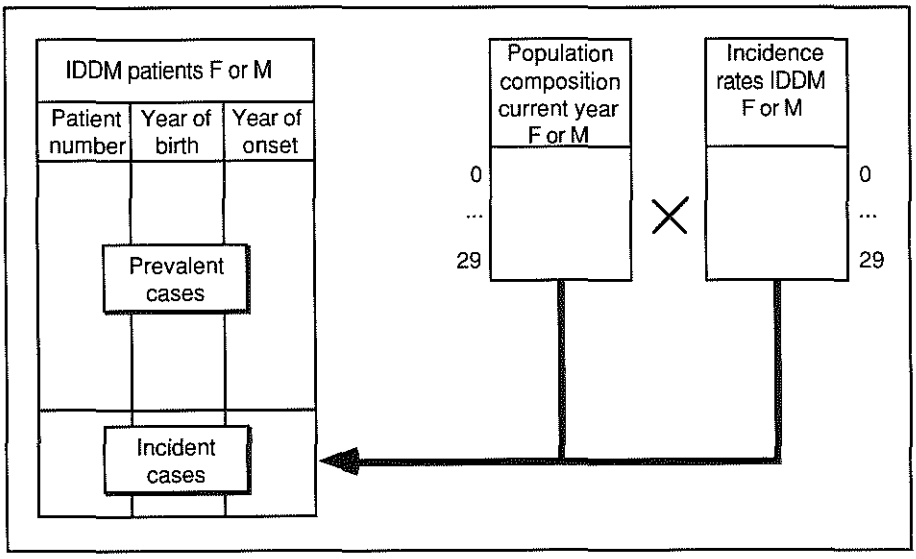

Figure 17.4 - Yearly growth of IDDM cohort; female or male patients

From the statistics regarding the composition of the population, the prognosis model annually selects the relevant numbers for the ages of zero to twenty-nine years. Figure 17.4 indicates schematically, how the number of annual incident cases of IDDM is determined through multiplying this thirty-element vector by another vector holding thirty age-specific incidence rates, either for men of for women. The new patients are individually added to the table of known IDDM patients by recording their patient number, year of birth and year of onset, which equals the current year. In this table, every patient occupies one line, also called *tuple* or *record* following the principles of relational databases [Date 81:223; Deen 85:138]. Regarding the incidence of NIDDM, the prognosis model applies the same technique to (1) the vector representing the population composition for the ages of 30 to 109 years and (2) the vector of NIDDM incidence rates for the same ages. An illustration of this calculation might be quite similar to figure 17.4 and is therefore omitted.

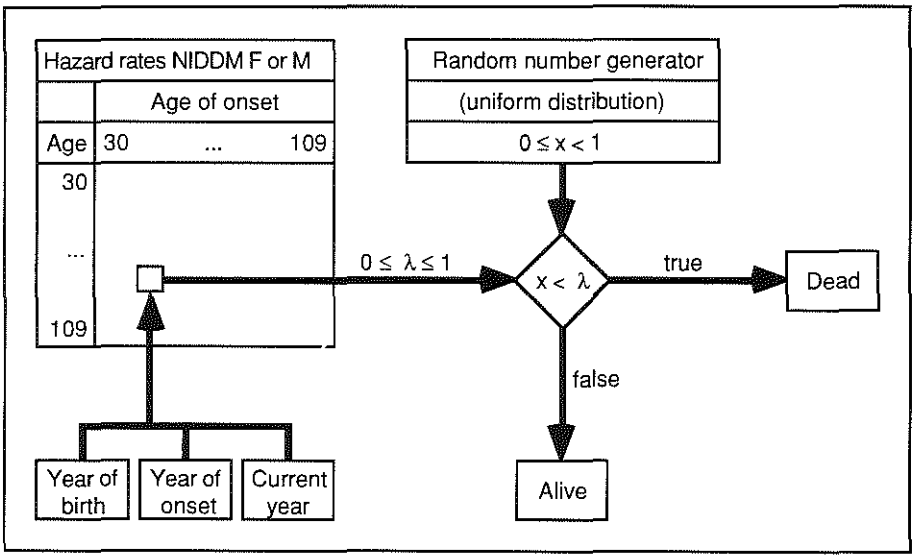

Figure 17.5 - Mortality module for NIDDM patients; female or male

Figure 17.5 presents the mortality module for NIDDM patients. Every patient traverses the module individually starting from the statistics recorded in the patient table, of which figure 17.4 sketches the structure. The patient's year of birth and year of onset plus the current year determine the patient's age and age of onset. These two outcomes refer to one particular element λ in a gender-specific table of hazard rates. Obviously, this table has elements only on the diagonal and below. Then, a random number x $\{0 \leq x < 1\}$ is drawn from a uniform distribution. The patient passes away, if x is smaller than λ. The IDDM mortality module is similar to the mortality module for

NIDDM patients, except for the fact that all IDDM patients have the same age of onset according to model assumptions. Therefore, the hazard rate λ only depends on age and gender. It is taken from a table holding one column of hazard rates.

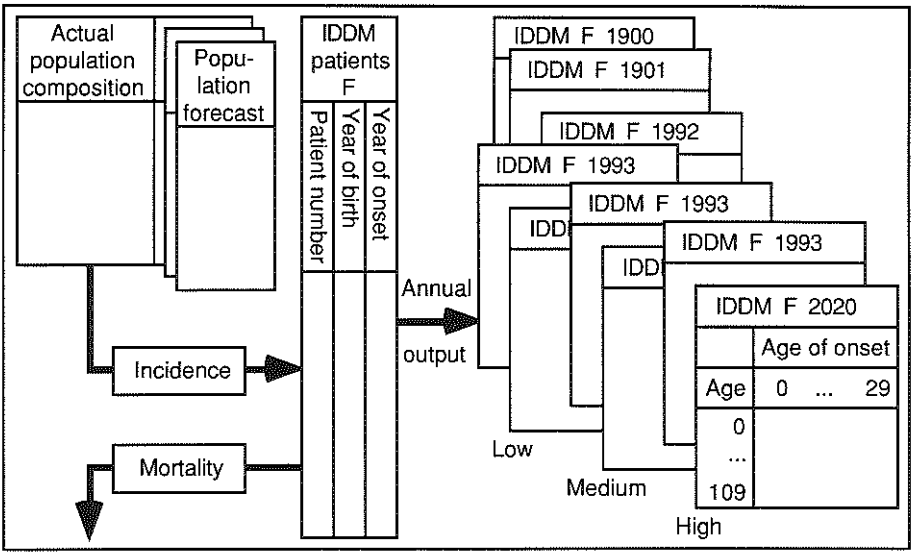

Figure 17.6 - Prevalence by year, population forecast variant, age and age of onset IDDM; female patients

From a bird's eye view, figure 17.6 illustrates, how the prognosis model produces data concerning the prevalence of IDDM among women. Demographic evidence for 1900 to 1992 plus three population forecasts - low, medium, high - for 1993 to 2020 provide details on the composition of the population in the Netherlands (cf. figure 17.3). Annually, the incidence module (cf. figure 17.4) adds new persons to the table of female IDDM patients, after which the mortality module (cf. figure 17.5) removes patients from the table. In this table, the model annually counts all patients by age and age of onset. These totals are recorded in a two-dimensional table - age, age of onset - according to the example presented by figure 17.6 for 2020 in the high variant of the population forecasts. In this scheme, the annual output may be divided into four parts. The first comprises the years 1900 to 1992, whereas the second, third and forth relate respectively to the low, medium and high variant of the population forecasts for the years 1993 to 2020. Similarly, the model is applied to male IDDM patients and to NIDDM patients. In the output tables for NIDDM patients, the ages and the ages of onset range from 30 to 109 years.

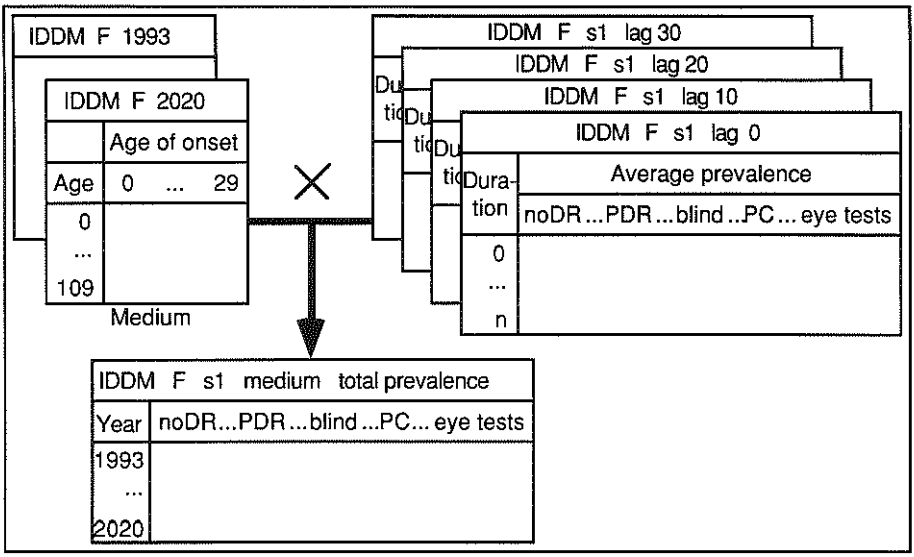

Figure 17.7 - Total prevalence 1993-2020; female patients; IDDM; s1; medium variant

Finally, figure 17.7 illustrates how the prognosis model determines the total prevalence of retinal disorders, visual disorders, ophthalmic examinations and laser treatments. The upper left corner presents the two-dimensional output tables for the years 1993 to 2020 which specify the prevalence of IDDM among women by age and by age of onset in the medium variant of the population forecasts (cf. figure 17.6). The upper right corner sketches the output tables of the IDDM simulations which were performed by the technique described in part B. The principal results have been presented in part C. In these tables, the original results are divided by the number of survivors to find the average prevalence. Because of spatial limitations, figure 17.7 mentions only a few classes of statistics. The abbreviation PC (PhotoCoagulation) indicates laser treatments. The four tables relate to cohorts of female IDDM patients who receive ophthalmic care according to scenario one with a time-lag of zero, ten, twenty or thirty years after the onset of IDDM. The statistics in the upper left corner are multiplied by the statistics in the upper right corner according to the technique presented in the previous section. In the output table, each line presents statistics on the total prevalence of eye disorders, examinations and treatments in one particular year of the period 1993-2020 for female IDDM patients who follow scenario one. The total IDDM output comprises thirty tables for two genders, five scenarios and three variants of population growth. For NIDDM patients, the prognosis models produces a similar number of output tables. The next chapter presents the main results.

18

Results

18.1 Introduction

Because of their abundance, the prognosis results prohibit integral presentation. Therefore, the present chapter makes rigorous selections directed to a confined set of subjects. The next paragraph illustrates the prevalence of IDDM and NIDDM in 1993 and 2020 for three variants of the population forecasts concerning the Netherlands. Subsequent sections try to answer the research questions presented in section 16.1. They accentuate (1) the prevalence of blindness in various scenarios of ophthalmic care, (2) the number of ophthalmic examinations and treatments as well as (3) personnel, matériel and financial aspects.

18.2 Prevalence of IDDM and NIDDM

Figure 18.1 presents the age composition for IDDM patients in 1993 following the medium variant of the population forecasts. Male patients are in a majority up to the age of some sixty years. Thereafter, the opposite is true because women have a higher life expectation. The number of IDDM patients reaches its maximum at the age of twenty-nine years: men 537 (0.40%), women 478 (0.38%). The percentages relate the IDDM cases to the number of 29-year-old men or women in the general population. According to the prognosis, 214 male IDDM patients are eighteen years old, which corresponds to 0.20% of the age group in the general population. This result is close to the findings by Vaandrager and associates [84] which revealed that the prevalence of DM among (male) military conscripts increased from 0.099% to 0.172% between 1960 and 1980. As appears from figure 18.1, the absolute prevalence of IDDM decreases from the age of thirty years. Versus outflow due to mortality, there is no inflow because new cases of DM are counted as NIDDM patients. From the age of thirty

years, the relative prevalence of IDDM also decreases as these patients face higher hazard rates than the general population.

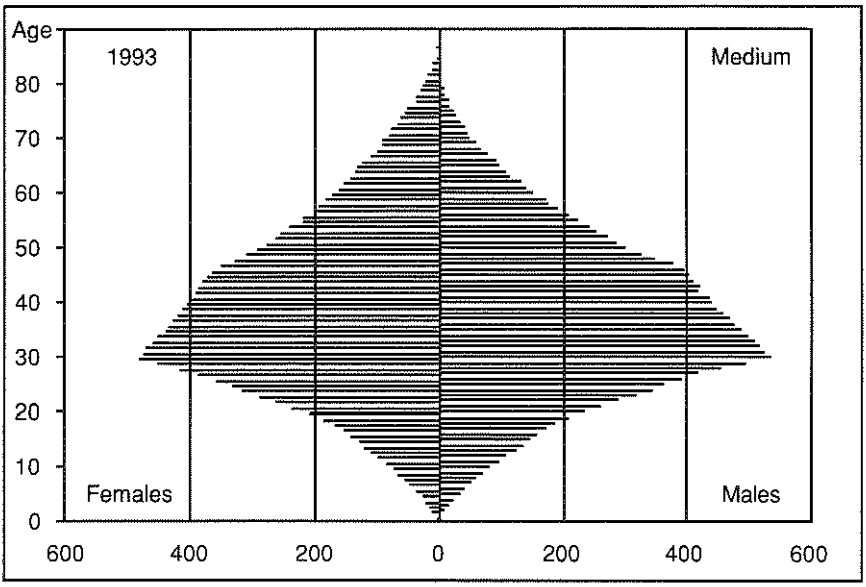

Figure 18.1 - Age composition of IDDM patients; 1993; medium variant

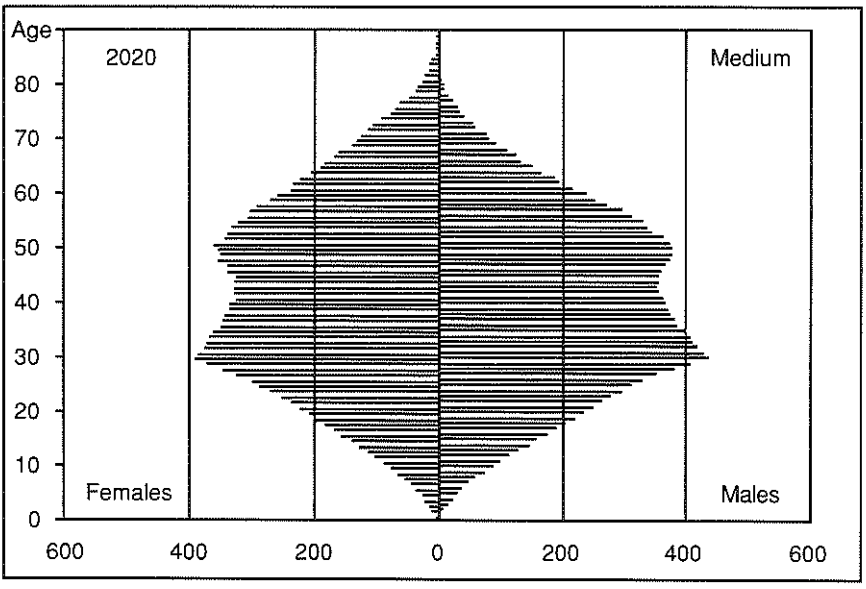

Figure 18.2 - Age composition of IDDM patients; 2020; medium variant

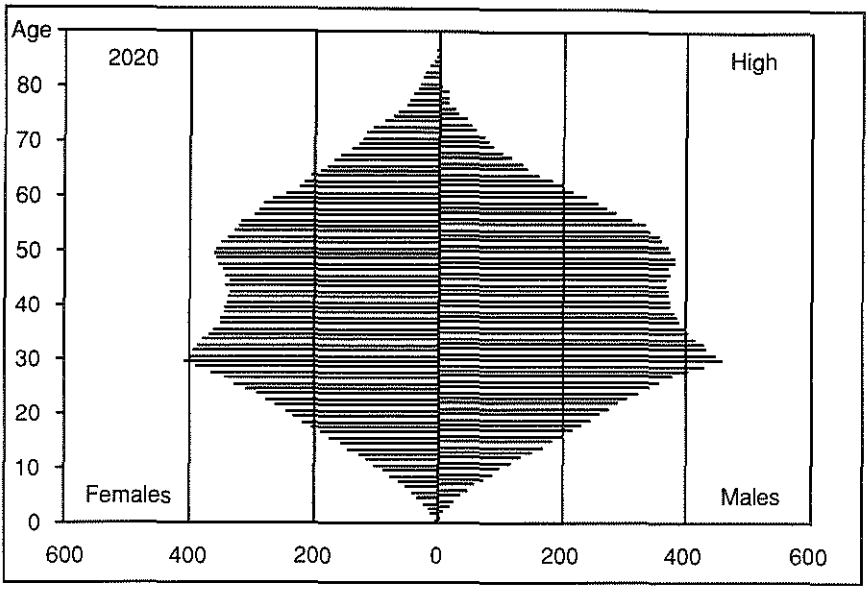

Figure 18.3 - Age composition of IDDM patients; 2020; high variant

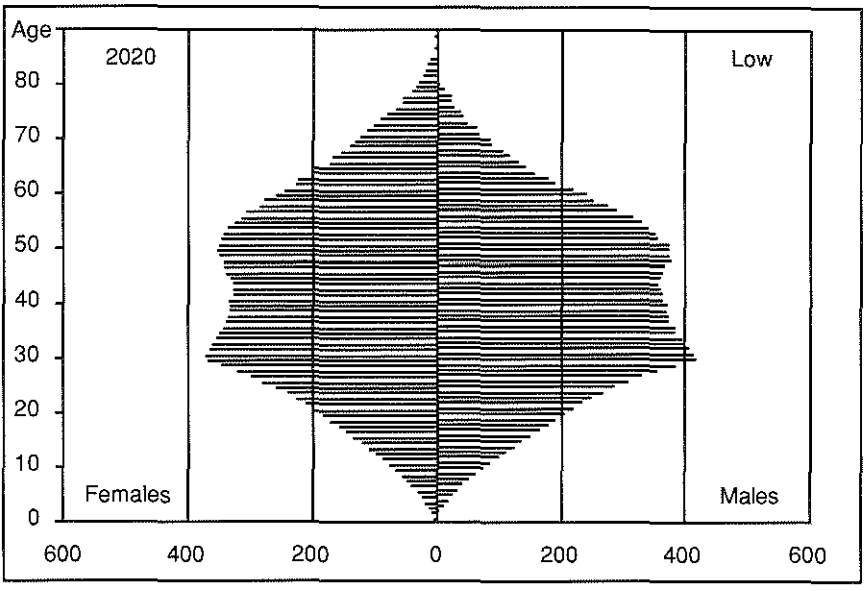

Figure 18.4 - Age composition of IDDM patients; 2020; low variant

In 1993, the low and the high variant lead to practically the same population composition as the medium variant. Diagrams for these two variants would hardly offer new information and are therefore omitted. In order to facilitate comparisons, the medium

variant for 2020 is presented immediately below the medium variant for 1993. The maximum prevalence of IDDM, at the age of twenty-nine years, decreases from 1993 to 2020 absolutely and relatively for the two sexes: men 440 (0.39%), women 389 (0.37%). The absolute mutations are remarkable. They reflect the fall in natality rates and the subsequent ageing of the population. The relative changes, on the contrary, are too small to be significant. Principally, this is the consequence of using constant incidence rates, so that changes in prevalence rates can only result from a peculiar age composition of the general population in previous years. Several studies however point to increases in the incidence of IDDM during recent decennia (cf. section 2.5). If this trend continues, the actual prevalence of IDDM in 2020 will exceed the prevalence pictured in figure 18.2. The most striking difference between figure 18.1 and figure 18.2 is the *"hump"* in the second diagram for ages near fifty years. It reflects an excessively high absolute prevalence following the birth bulge around 1970. This *"hump"* does not reflect changes in the incidence rates for the relevant age groups.

A comparison of the figures 18.2, 18.3 and 18.4 reveals that the differences between the three forecast variants are concentrated in the lower half of the diagrams. These differences relate to the age composition of the general population, which *"feeds"* the inflow of new IDDM patients. The three variants use dissimilar natality, mortality and migration rates to forecast the growth of the general population. Subsequent to demographic developments earlier this century, it is not surprising that mortality rates have a much smaller spread in the *Population Forecasts* than natality rates. Therefore, the differences between the three forecast variants for the general population primarily concern age groups affected by changes in natality rates, that is to say persons born in 1993 or later. Evidently, they are younger than twenty-eight years in 2020. This explains why the differences between the three forecast variants for IDDM patients are concentrated in younger age groups. For older ages, the differences are far less substantial. The numbers in table 18.1 confirm this. They reveal that the absolute prevalence of IDDM for men and women is respectively 4.0% and 3.6% greater in the high variant than in the medium variant, while 3.4% and 3.2% smaller in the low variant. For ages between zero and twenty-nine years, all these four differences approximate 10%, whereas they range from 14% to 18% for ages between zero and nine years. While prevalence differences are concentrated among patients younger than thirty years, the centre of gravity of ophthalmic is situated near ages of forty to forty-five years (cf. section 11.4). For this reason, the subsequent analysis of blindness and ophthalmic care centres on the medium variant.

Table 18.1 also enables one to compare 1993 with 2020. If the analysis is confined to the medium variant, the total number of female IDDM patients grows by 2.0%, while

the increase for men is limited to 0.2%. These rather small changes in the total prevalence are accompanied by relatively larger shifts in the age composition. In the five age categories for patients younger than fifty years, the absolute prevalence changes by −19% to +6%. In the older age groups, the absolute prevalence rises by 41% to 53%, apart from the increase by 333% in the small group of men aged eighty to eighty-nine years.

	Females				Males			
	1993	2020	2020	2020	1993	2020	2020	2020
Age	Medium	Medium	High	Low	Medium	Medium	High	Low
0-9	343	338	391	290	423	428	503	362
10-19	1384	1468	1652	1272	1613	1714	1945	1485
20-29	3514	2987	3208	2736	3901	3345	3582	3083
30-39	4372	3556	3656	3467	4851	3964	4080	3904
40-49	3553	3355	3443	3371	3863	3661	3755	3685
50-59	2204	3107	3132	3120	2213	3149	3151	3161
60-69	1223	1853	1830	1844	971	1487	1475	1459
70-79	504	740	720	748	254	384	374	385
80-89	58	89	96	92	3	13	7	6
≥ 90	0	0	0	0	0	0	0	0
Total	17155	17493	18128	16940	18092	18145	18872	17530

Table 18.1 - IDDM patients classified in ten age groups

Figure 18.5 pictures the prevalence of NIDDM in 1993 following the medium variant. Up to ages of some fifty-five years, there are more male than female patients. Thereafter, a substantial shift occurs, so that female patients overshadow male patients qua total number. This issue will also be considered in the subsequent analysis of table 18.2. The comparison of figure 18.5 to figure 18.6 reveals another remarkable fact. The total number of female and male patients increases considerably, namely by 43.0% and 51.8% respectively according to table 18.2. As these outcomes are determined by constant incidence rates, this development is caused by the ageing of the population. A further analysis of changes within age categories confirms this. Between 1993 and 2020, the absolute prevalence of NIDDM rises insignificantly for ages up to some fifty years. Older age groups, on the contrary, manifest almost explosive growth.

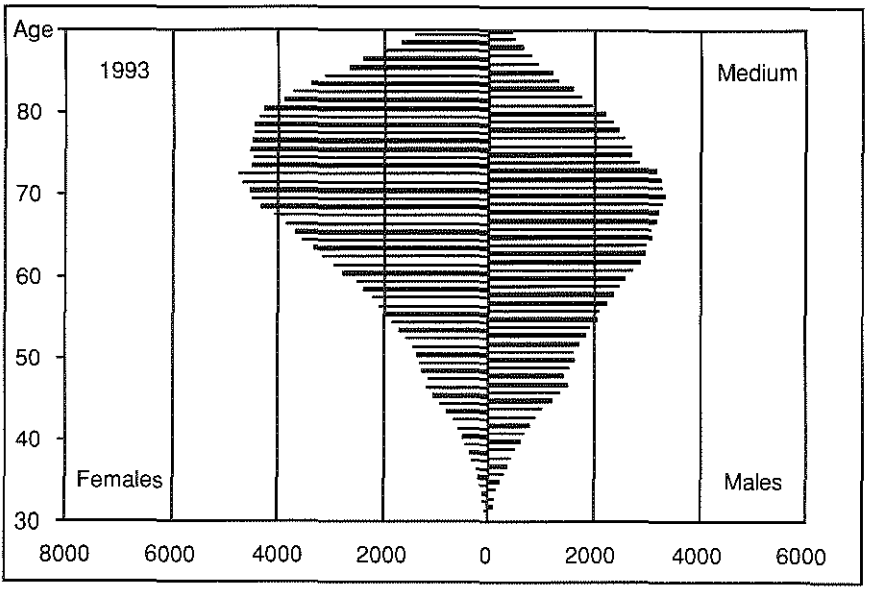

Figure 18.5 - Age composition of NIDDM patients; 1993; medium variant

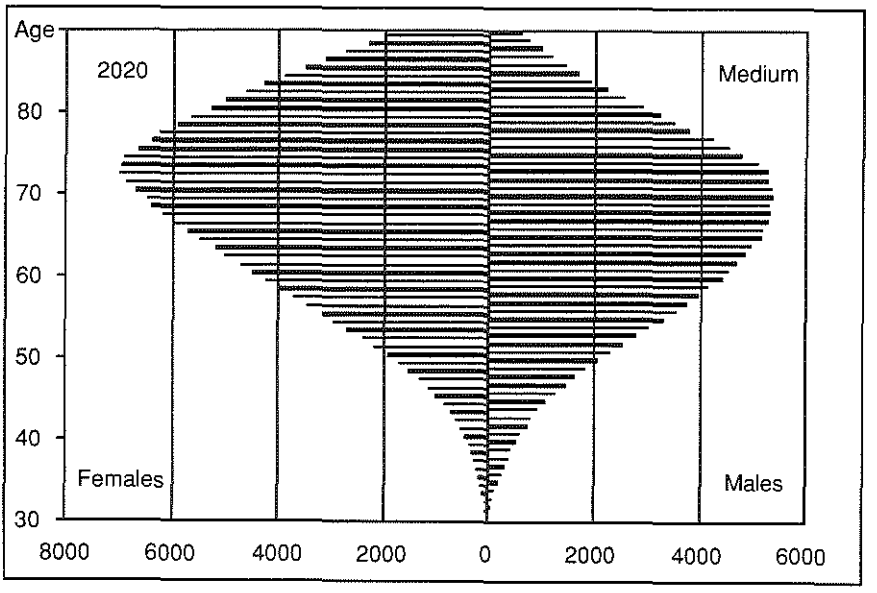

Figure 18.6 - Age composition of NIDDM patients; 2020; medium variant

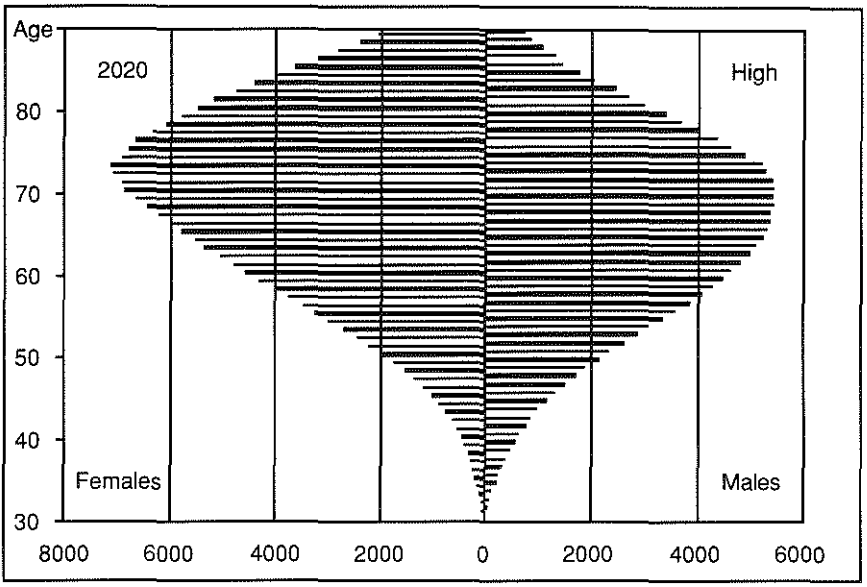

Figure 18.7 - Age composition of NIDDM patients; 2020; high variant

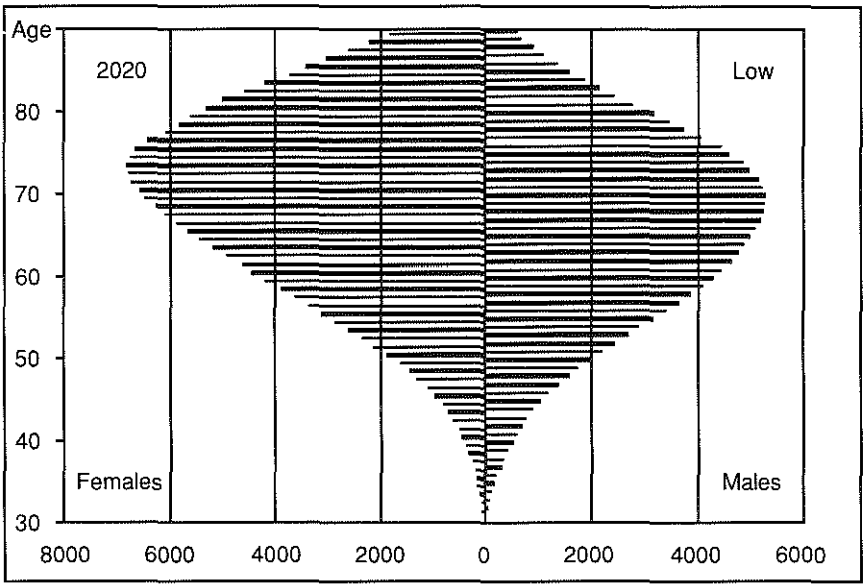

Figure 18.8 - Age composition of NIDDM patients; 2020; low variant

The figures 18.6, 18.7 and 18.8 fail to give indications of salient differences between the three forecast variants. This is confirmed by the sum totals in table 18.2. The total prevalence of NIDDM for men and women is respectively 3.0% and 2.3% greater in

the high variant than in the medium variant, while 2.9% and 2.0% smaller in the low variant. From a relative perspective, these differences are spread rather uniformly over the seven age categories.

	Females				Males			
Age	1993 Medium	2020 Medium	2020 High	2020 Low	1993 Medium	2020 Medium	2020 High	2020 Low
30-39	2011	1709	1783	1643	3001	2595	2706	2467
40-49	9366	9812	10072	9471	12289	12737	13242	12185
50-59	18956	30548	30997	29833	21206	34109	34808	33073
60-69	35999	55390	56287	54830	31095	50889	51875	50031
70-79	45087	65079	66314	64084	27869	45290	46552	43992
80-89	28389	36615	37781	35725	11430	16611	17675	15772
≥ 90	4116	6591	7221	5954	1123	1677	1931	1591
Total	143924	205744	210455	201540	108013	163908	168789	159111

Table 18.2 - NIDDM patients classified in seven age groups

Table 18.2 provides insight into the gender-composition of age categories. It reveals a general line that not only applies to 1993 but also to the three forecast variants in 2020. In the two younger age groups, men are in the majority, whereas the opposite is true in the five older age categories. This provokes a sizeable rupture which may be illustrated by the following statistics for 1993. In that year, there are 1.9% more male than female NIDDM patients younger than seventy years, but 92.0% more women than men of seventy years and older. Although the striking increase in the number of NIDDM patients between 1993 and 2020 has been emphasised before, it may be interesting to observe that the total number of NIDDM patients increases by 46.7% from 251,937 (1.65%) to 369,652 (2.18%) in the medium variant, while the total number of diabetic patients rises by 41.6% from 287,184 (1.88%) to 406,652 (2.40%). The sum totals are based on table 18.1 and table 18.2, while the percentages between brackets relate these numbers to the size of the general population. Meanwhile, the general population grows by 11.3% from 15,255,000 to 16,979,000 [CBS 91b].

Figure 18.9 sketches the relationship between the age of NIDDM patients and the average duration of the disorder. Between 1993 and 2020, only minor mutations appear. For ages of fifty to sixty-five years, the average duration is slightly higher for men than for women, which may be explained as follows. In the total population, the proportion of women is greater in older than in younger age groups, because of differences in life expectation. Consequently, far more new female than male cases of NIDDM are reported, even if the same incidence rates apply to both sexes. Among

female patients, the relatively large inflow of new cases affects the average duration of NIDDM downwards.

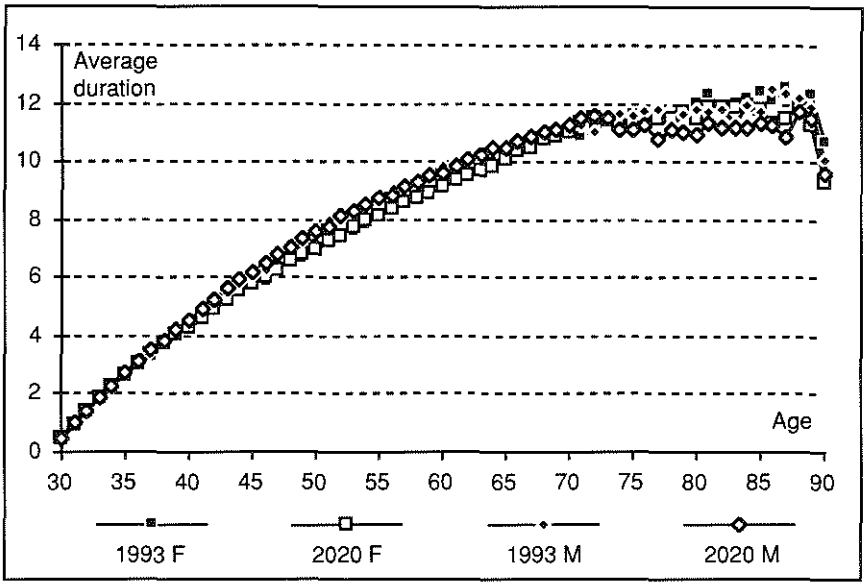

Figure 18.9 - Average duration of NIDDM in years by age; medium variant

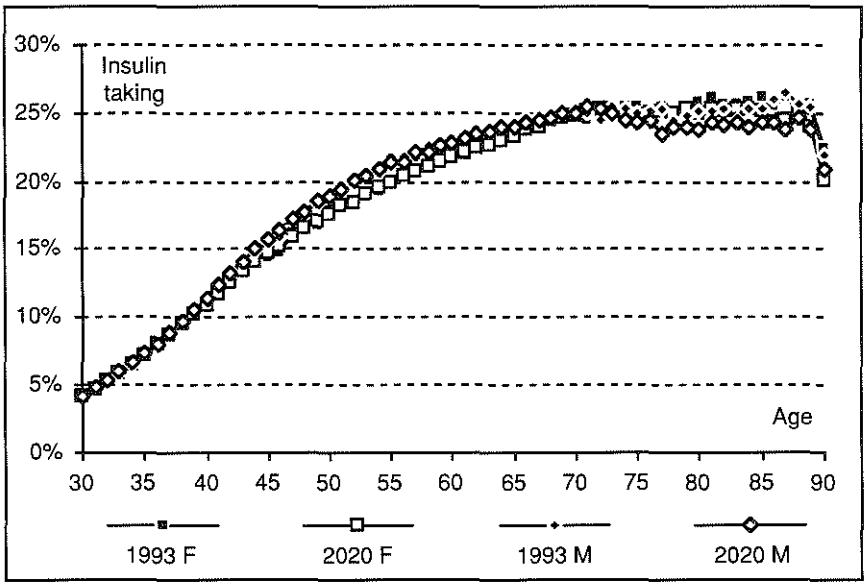

Figure 18.10 - Proportion of insulin taking NIDDM patients by age; medium variant

For most ages of seventy-five years and older, the differences between the curves for 1993 and 2020 are relatively large. The smaller average duration in 2020 may also be explained by a larger inflow following the ageing of the general population. According to figure 18.10, the proportion of insulin taking patients progresses according to a pattern that closely resembles the progression of the average duration. This may hardly create a surprise, because insulin taking is a function of the duration of NIDDM in the prognosis model (cf. section 16.3). Initially, less than 5% of all NIDDM patients take insulin, but this proportion rises to some 25% at higher ages.

18.3 Prevalence of Blindness

As appears from the previous section, the prevalence of IDDM or NIDDM in the low and high forecast variant deviates maximally 4% from the prevalence in the medium variant. Therefore, the subsequent analysis only considers the medium variant.

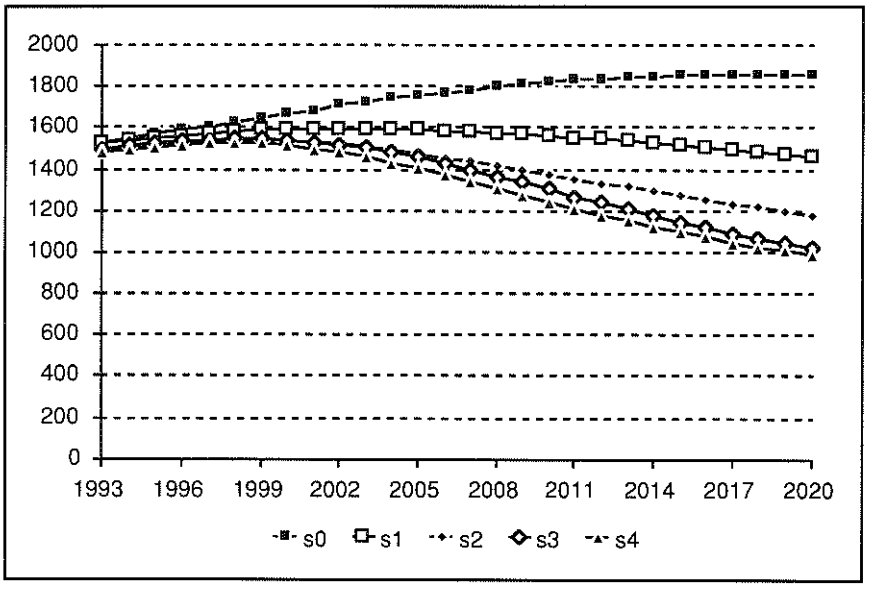

Figure 18.11 - Prevalence of blindness for IDDM patients by year; medium variant

From the assumption that diabetic patients are deprived of ophthalmic care before 1993, figure 18.11 illustrates the progression of the absolute prevalence of blindness among all female and male IDDM patients between 1993 and 2020 in five scenarios of ophthalmic care. Further analysis of the underlying statistics reveals that the four scenarios with ophthalmic care - s1, s2, s3, s4 - reduce the prevalence of blindness in

2020 by 21.0%, 36.4%, 44.9% and 46.7% respectively, as compared to scenario zero. From figure 18.11, one may infer that the curves for s1 and s2 diverge further from the curve for s0 after 2020. This is the outcome of the growth in the number of NIDDM patients.

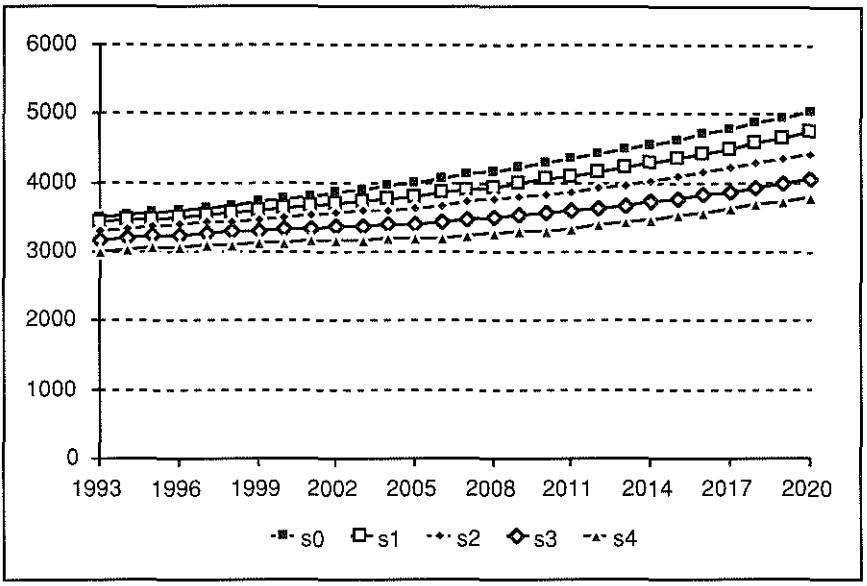

Figure 18.12 - Prevalence of blindness for NIDDM patients by year; medium variant

Figure 18.12 illustrates the progression in the prevalence of blindness among NIDDM patients. In 2020, the four scenarios with ophthalmic care - s1, s2, s3, s4 - enable one to prevent 6.2%, 12.5%, 19.7% and 24.9% of the blindness that occurs in scenario zero. For 2020, the statistics in table 18.3 are the basis of the curves in figure 18.11 and 18.12. They are differentiated by gender.

	IDDM				NIDDM			
	Females		Males		Females		Males	
s0	968	100.0%	886	100.0%	2950	100.0%	2105	100.0%
s1	764	78.9%	701	79.1%	2815	95.4%	1927	91.5%
s2	610	63.0%	569	64.2%	2623	88.9%	1799	85.5%
s3	539	55.7%	483	54.5%	2361	80.0%	1696	80.6%
s4	531	54.9%	457	51.6%	2237	75.8%	1562	74.2%

Table 18.3 - Prevalence of blindness in 2020; medium variant

18.4 Number of Ophthalmic Examinations and Treatments

For four scenarios with ophthalmic care, table 18.4 indicates how many ophthalmic examinations, fluorescein angiograms *(FA)*, focal plus grid laser treatments *(PC macula)* and panretinal / scatter laser treatments *(PC retina)* are performed for female and male IDDM patients in 1993 and 2020[1]. Each percentage in the table equals the quotient of the number to the left of it and the corresponding number in scenario one. For men and women, the number of ophthalmic examinations is approximately proportional to the intensity of ophthalmic care in 1993 and 2020. As we already know, this intensity has the proportion of 1:2:4:8 in the scenarios one, two, three and four. Thus, the progression of the number of ophthalmic examinations broadly corresponds to the previously presented results for IDDM patients (cf. table 11.4, section 11.4).

		Females				Males			
		1993		2020		1993		2020	
Eye tests	s1	4689	100%	4795	100%	4817	100%	4792	100%
	s2	9060	193%	9777	204%	9251	192%	9741	203%
	s3	18407	393%	19839	414%	18781	390%	19742	412%
	s4	37178	793%	40182	838%	37971	788%	39843	831%
FA	s1	1043	100%	692	100%	1077	100%	675	100%
	s2	1673	160%	641	93%	1705	158%	644	95%
	s3	2852	274%	760	110%	2808	261%	720	107%
	s4	5280	506%	940	136%	5013	465%	863	128%
PC macula	s1	294	100%	248	100%	314	100%	258	100%
	s2	342	116%	258	104%	356	113%	274	106%
	s3	380	129%	263	106%	404	129%	288	111%
	s4	394	134%	274	111%	431	137%	291	113%
PC retina	s1	448	100%	426	100%	458	100%	432	100%
	s2	557	125%	506	119%	595	130%	530	123%
	s3	644	144%	546	128%	696	152%	566	131%
	s4	721	161%	577	135%	793	173%	609	141%

Table 18.4 - Number of tests and treatments for IDDM patients; medium variant

As ophthalmic care is intensified, the growth in the number of fluorescein angiograms deviates remarkably from the outcomes of the IDDM simulation (cf. table 11.5, section

1 A focal treatment comprises two sessions, a grid treatment one session and a panretinal or scatter treatment four sessions (cf. section 8.8).

11.4), especially in 1993. In the IDDM simulation, the cumulative number of fluorescein angiograms deviates by −11% to +9% from scenario one in the scenarios two, three and four. In the prognosis, on the contrary, scenario four counts nearly five times as many fluorescein angiograms as scenario one in 1993. What are the reasons for this salient difference?

The prognosis is partly based on simulations where ophthalmic care is not delivered until several years after the onset of IDDM (cf. section 16.4). For quite some years after the first provision of ophthalmic care, far more fluorescein angiograms are performed in these simulations[2] than in simulations where ophthalmic care is provided without delay. To comprehend this, we might compare a situation with instant delivery of ophthalmic care to a situation where the delivery is delayed by thirty years. In the scenarios one, two, three and four, the number of fluorescein angiograms appears to be respectively 2.5, 5, 10 and 20 times as large in the latter as in the former situation during a period that covers some ten years after the first delivery of ophthalmic care. In those years, all retinal disorders approach their maximum prevalence rates (cf. figure 11.3 and figure 11.4, section 11.3). Consequently, eye examinations will frequently disclose retinal disorders that justify laser treatment. After such a diagnosis, a fixed proportion of the patients receive fluorescein angiography (cf. table 8.5, section 8.8). This explains the relatively large number of fluorescein angiograms in 1993. Between 1993 and 2020, all incident cases receive *"instant"* ophthalmic care, so that the proportion of patients with delayed ophthalmic care gradually declines. In 2020, the *"instant"* group is in the majority. This explains why the proportion of the number of fluorescein angiograms in the four scenarios then broadly corresponds to the proportion in the previously presented IDDM simulations (cf. table 11.5, section 11.4).

In 1993, the number of laser treatments follows the growth in the intensity of ophthalmic care at a comparatively larger distance as compared with the number of fluorescein angiograms. This has two reasons. Firstly, the delayed delivery of ophthalmic care is likely to delay the diagnosis of retinal disorders. ME and PDR may then have reached a phase that seriously impedes the effectiveness of laser treatment. Therefore, it is quite probable that the success rate has fallen below 5%, so that no laser treatment is given following model assumptions (cf. section 8.8). Secondly, ophthalmic examinations are not perfectly specific (cf. table 8.4, section 8.8). Thus, subsequent fluorescein angiograms may lead to more favourable diagnoses which provide no indication for photocoagulation.

2 The results of these simulations are omitted to save space.

In other words, the progression in the number of laser treatments broadly corresponds to the progression in the IDDM simulation (cf. table 11.7 and table 11.8, section 11.4). Obviously, there are some extra laser treatments in 1993 because of the backlog in the provision of ophthalmic care. In 2020, this backlog has disappeared. The proportions of the numbers in the four scenarios then closely resemble the outcomes of the IDDM simulation. Despite the conservative assumptions of the prognosis model, the intensification of ophthalmic care requires far less than proportional increases in the number of laser treatments in 1993, and even more so in 2020.

		Females				Males			
		1993		2020		1993		2020	
Eye tests	s1	32871	100%	41362	100%	24909	100%	32637	100%
	s2	58091	177%	78542	190%	43159	173%	61791	189%
	s3	58091	177%	78542	190%	80575	323%	120808	370%
	s4	215577	656%	305884	740%	156853	630%	239117	733%
FA	s1	4619	100%	5875	100%	3186	100%	4421	100%
	s2	7797	169%	9727	166%	5480	172%	7431	168%
	s3	7797	169%	9727	166%	9007	283%	10901	247%
	s4	19949	432%	21273	362%	14281	448%	16166	366%
PC macula	s1	614	100%	767	100%	420	100%	611	100%
	s2	1128	184%	1554	203%	766	182%	1142	187%
	s3	1722	280%	2384	311%	1183	281%	1813	297%
	s4	2105	343%	2915	380%	1502	357%	2236	366%
PC retina	s1	1131	100%	1530	100%	777	100%	1176	100%
	s2	1131	100%	1530	100%	1180	152%	1774	151%
	s3	2003	177%	2709	177%	1412	182%	2018	172%
	s4	2296	203%	3033	198%	1594	205%	2297	195%

Table 18.5 - Number of tests and treatments for NIDDM patients; medium variant

Table 18.5 presents few surprises as compared with the results of NIDDM simulations (cf. tables 14.5 to 14.8, section 14.4). According to the prognosis, the intensification of ophthalmic care is always followed by an increase in the number of tests and treatments which is, relatively speaking, comparable to the average of the mutations in NIDDM simulations. In these averages, the simulations for the eldest age of onset should have more weight, as the incidence of NIDDM increases significantly in later life (cf. table 16.1, section 16.3). It is surprising, that the number of fluorescein angiograms progresses *"normally"* in 1993 according to table 18.5, as opposed to table 18.4. What is the reason for this?

Firstly, the number of additional simulations is comparatively smaller for NIDDM than for IDDM patients (cf. table 16.3, section 16.4). Consequently, the additional simulations affect the outcomes of the NIDDM prognosis to a lesser extent. Secondly, the number of fluorescein angiograms deviate exponentially from the *"normal"* pattern, as the delivery of ophthalmic care is delayed. Therefore, the deviations in table 18.4 mainly result from simulations with a time-lag of thirty years. The maximum time-lag for NIDDM equals zero, ten and twenty years for the age of onset of 75, 55 and 35 years respectively. Thirdly, the incidence of NIDDM is concentrated in later life. This reduces the weight of additional simulations still further.

18.5 Personnel, Matériel and Financial Aspects

	Average number of tests/treatments per series	Average labour time per series of tests / treatments (minutes)		
		Ophthalmology	Assistance	Registration
Eye examination	1	15 (standard: 8)	—	5
Fluorescein angiography	1	20	10	—
Photocoagulation				
- panretinal / scatter	4	60	60	5
- focal	2	30	30	5
- grid	1	15	15	5

Table 18.6 - Average labour requirement per series of tests / treatments

Personnel resources are determined by the average labour requirement per series of tests and treatments which table 18.6 specifies by three labour categories[3]. For IDDM, the average labour requirement is multiplied by the number of tests and treatments indicated in table 18.4. In table 18.7, the total labour time for all IDDM patients in 1993 and 2020 is classified by four types of tests and treatments, four scenarios and three labour categories. Table 18.7 also mentions totals by scenario and labour category.

3 For this information, I acknowledge my gratitude to prof.dr. F. Hendrikse, Professor of Ophthalmology, Department of Ophthalmology, University of Limburg Medical School, Maastricht. The average duration of ophthalmic examinations for diabetes patients is fifteen minutes according to his experience. Official standards allocate eight minutes to these examinations without distinction between diabetic and not-diabetic patients. As eye disorders are significantly more frequent among diabetic patients than among other patients, the evidence from Hendrikse's practice is the basis of this prognosis.

		1993			2020		
		Ophthal-mology	Assist-ance	Regis-tration	Ophthal-mology	Assist-ance	Regis-tration
Eye tests	s1	2377	—	792	2397	—	799
	s2	4578	—	1526	4880	—	1627
	s3	9297	—	3099	9895	—	3298
	s4	18787	—	6262	20006	—	6669
FA	s1	706	353	—	456	228	—
	s2	1126	563	—	428	214	—
	s3	1887	943	—	493	247	—
	s4	3431	1715	—	601	300	—
PC macula	s1	228	228	51	190	190	42
	s2	262	262	58	200	200	44
	s3	294	294	65	206	206	46
	s4	309	309	69	212	212	47
PC retina	s1	906	906	75	858	858	71
	s2	1152	1152	96	1036	1036	86
	s3	1340	1340	112	1113	1113	93
	s4	1514	1514	126	1186	1186	99
Total	s1	4217	1487	918	3900	1275	913
	s2	7118	1977	1680	6544	1450	1757
	s3	12817	2577	3276	11707	1566	3437
	s4	24041	3539	6457	22005	1698	6815

Table 18.7 - Labour time in hours per year for IDDM patients; medium variant

According to table 18.7, the total labour time for ophthalmology decreases by 7.5% to 8.7% in the four scenarios between 1993 and 2020. For assistance, the reduction equals 14.2% to 52.0%, while the mutations range from –0.63% to 5.3% for registration. This is caused by the ageing of the general population and by the increasing emphasis on tests. Assumably, one year full-time employment comprises 1.200 net working-hours[4]. In 1993 and 2020, ophthalmic care for IDDM patients requires respectively 5.9 and 5.5 ophthalmologists (full-time employment) in scenario two,

4 In the Netherlands, there are 7 official holidays per year, including Liberation Day. Additionally, employees enjoy on average 24 holidays per year (estimate). Consequently, 229 working-days remain during 52 weeks with 5 working-days per week. As the sickness-leave rate equals some 8%, the yearly number of effective working-days is 210.68. At 38 working-hours per week, this corresponds to 1,601 working-hours per year. If 25% of the effective working-time is devoted to work-deliberation, meetings, training, management and remaining duties, the number of net working-hours per year equals 1,200.

versus 10.7 and 9.8 ophthalmologists in scenario three, while 20.0 and 18.3 ophthalmologists in scenario four.

		1993			2020		
		Ophthal-mology	Assist-ance	Regis-tration	Ophthal-mology	Assist-ance	Regis-tration
Eye tests	s1	14445	—	4815	18500	—	6167
	s2	25312	—	8437	35083	—	11694
	s3	34666	—	11555	49838	—	16613
	s4	93107	—	31036	136250	—	45417
FA	s1	2601	1301	—	3432	1716	—
	s2	4426	2213	—	5719	2860	—
	s3	5601	2801	—	6876	3438	—
	s4	11410	5705	—	12480	6240	—
PC macula	s1	388	388	86	517	517	115
	s2	710	710	158	1011	1011	225
	s3	1089	1089	242	1574	1574	350
	s4	1353	1353	301	1932	1932	429
PC retina	s1	1908	1908	159	2707	2707	226
	s2	2312	2312	193	3305	3305	275
	s3	3414	3414	285	4727	4727	394
	s4	3890	3890	324	5330	5330	444
Total	s1	19343	3597	5060	25155	4939	6507
	s2	32760	5234	8788	45118	7175	12195
	s3	44771	7304	12082	63014	9739	17356
	s4	109760	10948	31661	155991	13502	46290

Table 18.8 - Labour time in hours per year for NIDDM patients; medium variant

According to table 18.8, the results for NIDDM patients reveal a different pattern. Between 1993 and 2020, the labour time of ophthalmologists increases in the four scenarios by 30.0% to 42.1%. For assistance, the growth ranges from 23.3% to 37.3%, while registration requires 28.6% to 46.2% more labour time. Obviously, this is the result of ageing. In 1993 and 2020, ophthalmic care for NIDDM patients requires respectively 27.3 and 37.6 ophthalmologists (full-time employment) in scenario two versus 37.3 and 52.5 ophthalmologists in scenario three.

Table 18.9 indicates how many full-time employment positions are needed to provide all diabetic patients in 1993 and 2020 with the four scenarios of ophthalmic care. In 1993, scenario three requires some 12.5% of the capacity of ophthalmologists in the

Netherlands, as their number was estimated at 385 in 1989 [NOG 92:16]. This percentage rises to 16.2% in 2020, if the number of ophthalmologists were constant. The potential labour force is expected to grow by 7.9% from 1991 to 2020 in the medium variant of the *Population Forecasts* [CBS 92c]. If the number of ophthalmologists were to increase at the same velocity, there would be 415 ophthalmologists in 2020. The ophthalmic care for diabetic patients will then require 15.0% of their capacity.

	1993			2020		
	Ophthal-mology	Assist-ance	Regis-tration	Ophthal-mology	Assist-ance	Regis-tration
s1	19.6	4.2	5.0	24.2	5.2	6.2
s2	33.2	6.0	8.7	43.1	7.2	11.6
s3	48.0	8.2	12.8	62.3	9.4	17.3
s4	111.5	12.1	31.8	148.3	12.7	44.3

Table 18.9 - Number of full time employment positions in ophthalmic care for IDDM and NIDDM patients; medium variant

Matériel comprises instruments and accommodation. It would be superfluous to set up new tables for matériel requirements, because there exists a 1:1 relationship between the time spent by ophthalmologists on laser treatments and the time when laser equipment and accommodation should be available. Similarly, the matériel requirements for ophthalmic examinations and fluorescein angiograms can be determined.

From these findings, it might be possible to specify the estimated personnel and matériel requirements per hospital. This specification requires statistics, like the size and the age composition of each hospital's adherent population. Although these statistics are quite readily available, the specification meets complications. A hospital's actual adherence may differ from its administrative adherence, for instance because it attracts more patients by its excellent reputation. Some complications concern the attitude of general practitioners. For several reasons, doctors in one area may pay relatively more attention to diabetes, while physicians in another area may be more observant of cancer. Furthermore, some general practitioners preferably perform ophthalmic examinations themselves, whereas others rather refer patients to ophthalmic clinics. Complications may also result from *"spontaneous"* specialisation. If a clinic happens to be the first in a certain area to install ophthalmic laser equipment, it may attract many patients from neighbouring clinics, even after this equipment has also been installed elsewhere. In 1992, the diffusion of laser equipment was confined to 68.4% of the Dutch general hospitals [Vondeling 93]. These, besides other, complications cause the demand for ophthalmic care in a particular clinic to deviate from the national trend. Therefore, a

specification of estimated personnel and matériel requirements per hospital would require additional research beyond the limits of this study. This research could be based on the national estimates in the tables 18.7 to 18.9.

		IDDM		NIDDM		Total	
		1993	2020	1993	2020	1993	2020
Eye tests	s1	ƒ 455,607	ƒ 459,466	ƒ 2,769,111	ƒ 3,546,386	ƒ 3,224,717	ƒ 4,005,852
	s2	ƒ 877,570	ƒ 935,405	ƒ 4,852,387	ƒ 6,725,490	ƒ 5,729,957	ƒ 7,660,895
	s3	ƒ 1,782,213	ƒ 1,896,915	ƒ 6,645,545	ƒ 9,553,860	ƒ 8,427,757	ƒ 11,450,775
	s4	ƒ 2,228,170	ƒ 2,372,749	ƒ 11,042,543	ƒ 16,159,251	ƒ 13,270,713	ƒ 18,532,000
FA	s1	ƒ 655,108	ƒ 422,390	ƒ 2,412,354	ƒ 3,182,489	ƒ 3,067,462	ƒ 3,604,879
	s2	ƒ 1,044,040	ƒ 397,323	ƒ 4,103,851	ƒ 5,303,277	ƒ 5,147,891	ƒ 5,700,600
	s3	ƒ 1,749,784	ƒ 457,366	ƒ 5,193,997	ƒ 6,375,845	ƒ 6,943,781	ƒ 6,833,211
	s4	ƒ 3,181,448	ƒ 557,110	ƒ 10,580,372	ƒ 11,572,323	ƒ 13,761,819	ƒ 12,129,433
PC macula	s1	ƒ 896,323	ƒ 746,302	ƒ 1,525,638	ƒ 2,031,881	ƒ 2,421,961	ƒ 2,778,183
	s2	ƒ 1,029,865	ƒ 784,723	ƒ 2,791,853	ƒ 3,975,008	ƒ 3,821,718	ƒ 4,759,731
	s3	ƒ 1,156,130	ƒ 811,930	ƒ 4,282,519	ƒ 6,188,808	ƒ 5,438,649	ƒ 7,000,738
	s4	ƒ 1,216,937	ƒ 833,454	ƒ 5,318,826	ƒ 7,595,917	ƒ 6,535,764	ƒ 8,429,371
PC retina	s1	ƒ 1,674,804	ƒ 1,586,366	ƒ 3,528,421	ƒ 5,004,402	ƒ 5,203,225	ƒ 6,590,768
	s2	ƒ 2,130,351	ƒ 1,915,790	ƒ 4,274,263	ƒ 6,110,629	ƒ 6,404,614	ƒ 8,026,418
	s3	ƒ 2,476,760	ƒ 2,057,098	ƒ 6,312,972	ƒ 8,740,227	ƒ 8,789,732	ƒ 10,797,324
	s4	ƒ 2,799,085	ƒ 2,193,060	ƒ 7,193,045	ƒ 9,855,290	ƒ 9,992,129	ƒ 12,048,350
Total	s1	ƒ 3,681,841	ƒ 3,214,524	ƒ 10,235,524	ƒ 13,765,158	ƒ 13,917,365	ƒ 16,979,682
	s2	ƒ 5,081,826	ƒ 4,033,241	ƒ 16,022,354	ƒ 22,114,403	ƒ 21,104,180	ƒ 26,147,644
	s3	ƒ 7,164,886	ƒ 5,223,309	ƒ 22,435,033	ƒ 30,858,740	ƒ 29,599,919	ƒ 36,082,048
	s4	ƒ 9,425,640	ƒ 5,956,373	ƒ 34,134,785	ƒ 45,182,781	ƒ 43,560,425	ƒ 51,139,154
Total per patient	s1	ƒ 104	ƒ 90	ƒ 41	ƒ 37	ƒ 48	ƒ 42
	s2	ƒ 144	ƒ 113	ƒ 64	ƒ 60	ƒ 73	ƒ 65
	s3	ƒ 203	ƒ 147	ƒ 89	ƒ 83	ƒ 103	ƒ 89
	s4	ƒ 267	ƒ 167	ƒ 135	ƒ 122	ƒ 152	ƒ 126

Table 18.10 - Undiscounted direct costs of ophthalmic care at 1992 charges; medium variant

Table 18.10 presents the total direct costs of ophthalmic care in 1993 and 2020 for IDDM and NIDDM patients. The costs are based on the ophthalmic care charges in the Netherlands for 1992 (cf. table 9.2, section 9.6) and the number of treatments in table 18.4 and table 18.5. The total costs per IDDM patient are in all scenarios larger than per NIDDM patient.

	IDDM	NIDDM
s1	*f* 8,253	*f* 43,939
s2	*f* 5,970	*f* 34,956
s3	*f* 6,274	*f* 30,945
s4	*f* 6,880	*f* 35,967

Table 18.11 - Direct costs per year vision gain in 2020; medium variant

Nonetheless, ophthalmic care is more cost-effective for IDDM than for NIDDM patients. This is disclosed by the cost-effectiveness ratios in table 18.11, where *"vision gain"* represents the reduction in blindness as compared with scenario zero. Scenario two minimises the direct costs per year vision gain for IDDM patients and scenario three for NIDDM patients.

		IDDM		NIDDM	
			Benefits minus costs		Benefits minus costs
Direct costs	s1	*f* 90.20		*f* 37.24	
	s2	*f* 113.17		*f* 59.82	
	s3	*f* 146.57		*f* 83.48	
	s4	*f* 167.14		*f* 122.23	
Benefits human capital approach	s1	*f* 1,396.24	*f* 1,306.04	*f* 20.06	-*f* 17.18
	s2	*f* 2,059.57	*f* 1,946.40	*f* 59.59	-*f* 0.23
	s3	*f* 2,356.99	*f* 2,210.43	*f* 87.33	*f* 3.85
	s4	*f* 2,375.36	*f* 2,208.22	*f* 91.43	-*f* 30.80
Benefits friction costs technique	s1	*f* 140.46	*f* 50.26	*f* 3.34	-*f* 33.90
	s2	*f* 218.88	*f* 105.71	*f* 8.00	-*f* 51.83
	s3	*f* 256.40	*f* 109.84	*f* 12.02	-*f* 71.47
	s4	*f* 260.20	*f* 93.06	*f* 13.89	-*f* 108.34

Table 18.12 - Costs and benefits per patient in 2020; medium variant

Table 18.12 enables to compare the direct costs with the benefits per patient in 2020. For IDDM patients, the balance of benefits and costs is always positive, even according to the more conservative *friction costs technique*. Scenario three offers the most favourable balance: *f* 109.84 (≈ *f* 256.40 – *f* 146.57). The *human capital approach* yields more favourable balances, which also reach a maximum in scenario three: *f* 2,210.43 (≈ *f* 2,356.99 – *f* 146.57). All balances for NIDDM are negative, except for scenario three in the *human capital approach*: *f* 3.85 (= *f* 87.33 - *f* 83.48). This is hardly surprising. In 2020, 3.2% of the NIDDM patients are less than forty-five years old, 35.5% are forty-five to sixty-four years old and 61.3% are older than sixty-

four years (cf. figure 18.6, section 18.2). Moreover, the average duration of NIDDM hardly exceeds twelve years (cf. figure 18.9, section 18.2). According to the results for NIDDM simulations presented in part D, the cost-effectiveness ratios deteriorate significantly, as the age of onset rises. If shortages of ophthalmic care make choices unavoidable, it might be necessary to differentiate by age of onset.

Table 18.12 finishes the presentation of results. Surprisingly enough, discounting is omitted, although part C and part D use three discount rates. The reason follows: the IDDM and NIDDM simulations cover a considerable number of years when costs, effects and benefits do not progress synchronously. Consequently, the omission of discounting distorts the assessment of costs, effects and benefits. The prognosis faces a similar sequence of costs, effects and benefits. Nevertheless, it may be considered from a different perspective. During the first years of the period 1993-2020, tests and treatments are primarily directed to eliminate the backlog which results from the assumption that patients receive no ophthalmic care before 1993. Thereafter, the progression of costs, effects and benefits tends to stabilise, although the ageing of the general population disturbs developments for NIDDM patients. After the starting period, the cost-effectiveness may be analysed by comparing (1) the flow of direct costs of ophthalmic care with (2) the flow of effects and benefits related to changes in the prevalence of blindness, in labour productivity and in costs of disability facilities. These flows materialise in the same year.

Analogously to the financing of social security systems, the latter approach may be compared with a system of transfer payments, where expenses are covered by current contributions. Capital accumulation is typically absent in these systems. At the opposite, there are systems based on investment funds, like pension funds. Members may individually accumulate capital to secure income after retirement because of advanced age or disablement [Douben 86:142-3]. The relationship between the flows of costs, effects and benefits regarding ophthalmic care is closely allied to systems of transfer payments, because insurance premiums, payroll deductions and tax payments are the principal pecuniary sources of the Dutch health care system. Disability facilities are financed similarly. By preventing blindness, ophthalmic care may promote increases in labour productivity and income. This is automatically followed by extra payroll deductions and tax payments to the benefit of the health care sector, including disability facilities. Finally, equipment costs are a minor part to the total costs. Consequently, this chapter is rather based on a system of transfer payments where payments and expenses tend to coincide in time. Therefore, the prognosis does not require discounting.

The next chapter presents concluding remarks on the outcomes of the prognosis.

19

Concluding Remarks

19.1 Introduction

Nobody can foretell future events. This observation raises the question, whether the outcomes of the prognosis offer sufficient support to answer the research questions presented in section 16.1 convincingly. In the prognosis, there are two major sources of uncertainty. The first concerns the IDDM and NIDDM simulations which constitute important cornerstones. In the chapters ten, twelve, thirteen and fifteen, the trustworthiness of these simulations has been an prominent subject of discussion. Therefore, it seems unnecessary to reconsider this issue. The second source of uncertainty originates from future demographic, epidemiologic, medico-technological and financial developments.

Regarding the expected growth of the general population, the prognosis refers to the most authoritative predictions, namely the *Population Forecasts* by the Netherlands Central Bureau of Statistics. Moreover, the prognosis does not reach beyond 2020, whereas the *Population Forecasts* go as far as 2050. Consequently, all persons who develop NIDDM in 2020 or earlier have been born already. Recent decennia have demonstrated that hazard rates tend to stabilise. Therefore, the size of the general population aged thirty years or older may be estimated rather accurately until 2020, except for disturbances in migration flows.

Obviously, there exists less certainty about the progression of the general population younger than thirty years, not the least because birth rate figures have manifested considerable fluctuations in recent decennia. However, table 18.1 (section 18.2) indicates that the prevalence of IDDM in the low and the high variant of the *Population Forecasts* differs in 2020 respectively by –3.3% and 3.8% from the medium variant. These percentages are the limits of an interval wherein the level of statistical significance unquestionably exceeds 68% [Beer 92b].

Epidemiologic developments provide less certainty, because several studies indicate that the incidence of IDDM has risen in recent decades (cf. section 2.5). Nevertheless, the prognosis uses constant incidence rates for two reasons. First, it is not certain that incidence rates will continue to increase in the future. Second, the prognosis *coûte que coûte* wants to avoid excessively optimistic forecasts. However, if incidence rates of IDDM continue to rise in the future, the prognosis underestimates the potential effects of ophthalmic care for IDDM patients. Similar observations apply to NIDDM.

Medical technology nourishes high hopes. According to some investigators, it should be possible to offer IDDM patients preventive therapy by the turn of the century. This treatment will stop the destruction of β-cells in the islets of Langerhans [Atkinson 90]. Moreover, in the near future conclusive evidence will appear on the relationship between metabolic control and the probability of complications [DCCTRG 86][1]. Finally, laser treatment may become more effective in preventing moderate vision and blindness. Advances in medical technology affect the effectiveness of ophthalmic care in different directions. Improvements in ophthalmic screening and treatment techniques will benefit the effectiveness, whereas achievements in the prevention of DM and DR may reduce the effectiveness. At present, more precise statements on this issue seem speculative. Consequently, the prognosis is based on existing medical techniques.

For financial aspects, the prognosis might use forecasts on prices and charges. In a retrospective analysis however, the forecast margins for the general price-level of private consumption equalled –2.4% and +1.0% in the medium-term forecasts (covering four to five years) by the Dutch Central Planning Bureau[2] for the period 1966-1990 [Westerhout 90]. The actual average annual increase in the general price level was less than 4%. In other words, the interval delimited by the forecast margins is nearly as large as the average annual growth rate. Furthermore, it is quite likely that the general price-level can be predicted more accurately than prices of specific goods and services. Moreover, Mandelbrot has highlighted fundamental limitations of economic forecasting in general and prices in particular [Gleick 87:20, 83-4]. Consequently, predictions on

1 Recent newspaper-reports announce a forthcoming article in the *New England Journal of Medicine* on outcomes of the *Diabetes Control and Complications Trial* [NRC/Handelsblad, June 18th, 1993; De Volkskrant, June 19th, 1993]. According to the second report, intensive metabolic control was found to reduce retinal complications by 27% to 45% among more than 1,400 American and Canadian IDDM patients who were studied for 6.5 years on average.

2 These forecasts indicate annual changes expressed in percentages. The two margins limit an area that holds two thirds of the actual changes. These margins are represented by percentages that relate to the price-level in the previous year. The *Dutch Central Planning Bureau* is specialised in macro-economic forecasting.

the progression of prices and charges until 2020 are purely speculative. This compels the prognosis to use actual prices and charges.

At first sight, this seems a poor strategy, because prices and charges will undoubtedly differ considerably in 2020 from 1992. Some considerations mitigate the drawbacks of this approach. For comparisons of time series, the quotient of costs and benefits may be more interesting than their absolute level. Quotients enable to emphasise real developments and to neglect disturbances caused by inflation that affect costs and benefits equally. Moreover, the progression of wages in recent decades reveals that wage ratios of various types of labour are far more constant than absolute real wage levels. Labour costs constitute a sizeable component of the costs and benefits under consideration. Therefore, it seems plausible that the ratios for 1992 present useful indications for the ratios in 2020. Finally, using constant prices and charges partly counterbalances the omission of discounting.

These observations reaffirm that the prognosis faces considerable uncertainty. Therefore, the model does not pretend to foretell future events exactly. The prognosis merely wants to indicate the lower limit of the cost-effectiveness of ophthalmic care for diabetic patients. This explains the conservative approach regarding missing, contradictory or imprecise data. Consequently, the actual progression will rather deviate favourably than unfavourably from the outcomes of the prognosis. Demographic and epidemiologic parameters are the main cornerstones of the model. They provide a higher degree of certainty than technological and financial developments. For that reason, the prognosis has a level and a time-interval of certainty that is situated somewhere in between weather forecasts and predictions on movements of celestial bodies. It would however be speculative to indicate the position of the prognosis more precisely in this spectrum of certainty. Following these general observations, the next sections present more specific remarks.

19.2 IDDM

According to figure 18.1, figure 18.2 and table 18.1, the average age of IDDM patients increases between 1993 and 2020. Table 19.1 quantifies this evolution. It also mentions the average duration and the average age of onset. Expressed in years, the changes are larger for women than for men. The rise in the average duration approximately equals the increase in the average age, because the average age of onset increases only slightly. The latter mutation results from the ageing of the general population and the attendant shift towards a higher age of the numerical centre of gravity in

the age group below thirty years. As incidence rates remain constant, this raises the average age of onset.

	Females			Males		
			2020 -/-			2020 -/-
	1993	2020	1993	1993	2020	1993
Average age (years)	38.36	41.14	2.78	36.62	38.90	2.28
Average duration (years)	22.19	24.74	2.55	20.72	22.81	2.09
Average age of onset (years)	16.17	16.40	0.23	15.90	16.09	0.19

Table 19.1 - Average age, duration and age of onset; IDDM; medium variant

For ophthalmic care, the increases in the average duration are the most relevant changes, as the duration of IDDM constitutes the main risk factor for retinal and visual disorders (cf. e.g. section 3.4). Moreover, the severity of DR is the only determinant of the frequency of eye tests in each scenario (cf. table 8.1, section 8.4). One might therefore suspect that IDDM patients demand more ophthalmic care in 2020 than in 1993. This expectation should be tested with some precaution by results of the prognosis, because the model assumes that patients receive no eye care before 1993. In subsequent years, backlogs require additional care. The earlier years of the prognosis are therefore left out of consideration. Between 2000 and 2020, the annual totals of the four care components - ophthalmic examinations, fluorescein angiograms, focal/grid laser treatments, panretinal/scatter treatments - are approximately constant in each of the four scenarios of eye care. During that period, the average duration of IDDM increases by 1.3 years from 22.5 to 23.8 years. According to the figures 11.13, 11.14, 11.16 and 11.17 in section 11.4, this mutation is situated in an interval where the numbers of fluorescein angiograms and laser treatments approach their maximum. This explains why the annual totals are stable.

According to figure 18.11, the absolute prevalence of blindness does not reach stability by 2020 in the scenarios one to four. Nonetheless, the comparison of table 18.3 (section 18.3) with table 11.2 (section 11.3) discloses the following for all scenarios with eye care: In the prognosis, virtually the same proportion of patients are protected from blindness as in the IDDM simulation. The results of the prognosis also indicate that the prevalence of blindness falls sharply as eye care is intensified, although the number of laser treatments rises only moderately (cf. table 18.4, section 18.3). This explains, why increases in direct costs fall short of rises in the intensity of ophthalmic care (cf. table 18.12, section 18.5). From scenario one to scenario three and four, they grow respectively by 62.5% and 85.3% per patient, although the intensity of eye care rises by 300% and 700%. Therefore, it does not come as a surprise that the ratio of

direct costs and vision gain is more favourable in scenario two, three and four than in scenario one (cf. table 18.11, section 18.5).

Although scenario two minimises the direct costs per year vision gain, it may be worthwhile to consider scenario three as an alternative for the same reasons that were presented in section 12.4. As we already know, many patients fail to observe recommended screening guidelines. Advising scenario three might enable us to realise at least scenario two among the majority of patients. The direct costs per year vision gain are *f* 304.- higher in scenario three than in scenario two, but scenario three protects 157 patients more from blindness (table 18.3, section 18.3). Scenario three also seems justifiable from a macro-economic perspective, as it leads to the most favourable balance of direct costs and benefits according to the *human capital approach* and the *friction costs technique*. In both balances, benefits exceed costs (cf. table 18.12, section 18.5). Apart from that, the American and Dutch guidelines go partly as far as scenario four. Jointly, the *American College of Physicians,* the *American Diabetes Association* and the *American Academy of Ophthalmology* recommend annual ophthalmic examinations, starting five years after the onset of IDDM [ACP 92]. In the Netherlands, the national associations of ophthalmologists *(Nederlands Oogheelkundig Gezelschap)*, general practitioners *(Nederlands Huisartsen Genootschap)*, internists *(Nederlandsche Internisten Vereeniging)*, diabetes investigators *(Nederlandse Vereniging voor Diabetes Onderzoek)* and diabetic patients *(Diabetes Vereniging Nederland)* have agreed on nearly identical guidelines [Hendrikse 92].

19.3 NIDDM

According to table 19.2, the key characteristics of the female group are remarkably stable, whereas the male group faces ageing and an increase in the age of onset. As the average duration of NIDDM remains nearly constant for all patients, the proportion of insulin taking patients changes only slightly.

	Females			Males		
			2020 -/-			2020 -/-
	1993	2020	1993	1993	2020	1993
Average age (years)	69.33	69.42	0.08	64.42	65.46	1.04
Average duration (years)	9.82	9.72	-0.10	9.38	9.45	0.07
Average age of onset (years)	59.51	59.69	0.18	55.04	56.01	0.97

Table 19.2 - Average age, duration and age of onset; NIDDM; medium variant

The changes indicated in table 19.2 shrink into insignificance beside the growth by 46.7% in the number of NIDDM patients between 1993 and 2020 (cf. figures 18.5 and 18.5, table 18.2, section 18.2). The demand for ophthalmic care rises approximately in the same proportion (table 18.8, section 18.5). It is evenly spread over ophthalmic examinations, fluorescein angiograms and various types of laser treatments. The absolute prevalence of blindness increases between 1993 and 2020 in all scenarios, following the sizeable growth in the number of NIDDM patients (cf. figure 18.12, section 18.3). In 2020, ophthalmic care enables us to prevent approximately the same proportion of blindness in the prognosis as in the simulation for NIDDM patients, provided that the comparison concerns groups with a similar composition regarding age and age of onset (cf. table 14.2, section 14.3 and table 18.3, section 18.3). Among NIDDM patients, relatively less blindness can be prevented than among IDDM patients. The number of fluorescein angiograms and laser treatments also progresses less favourably as the intensity of ophthalmic care rises (cf. table 18.5, section 18.3).

From the preceding observations, it evidently follows that ophthalmic care for NIDDM patients is characterised by a less favourable ratio of costs and benefits. The minima in table 18.11 (section 18.5) indicate that one year sight gain is over five times more expensive than for IDDM patients. Benefits nearly always fail to offset direct costs, even in the *human capital approach* (cf. table 18.12, section 18.5). Consequently, financial considerations provide insufficient support to justify ophthalmic care for NIDDM patients. However, this statement elicits at least two marginal notes. Firstly, it concerns all NIDDM patients without distinction by age of onset. The NIDDM simulations reveal however, that the costs per year vision gain increase as the age of onset rises, whereas benefits fall (cf. table 14.15, section 14.7). In the prognosis, the average age of onset ranges from fifty-five to sixty years. Therefore, it would be incorrect to infer from the outcomes of the prognosis, that ophthalmic care has a rather unfavourable cost-effectiveness ratio for all NIDDM patients. Secondly, economic arguments are of minor importance beside humanitarian aspects. The latter explain why the American and Dutch associations, mentioned at the end of the previous paragraph, also recommend annual ophthalmic examinations for NIDDM patients. Patients should have their first eye test shortly after the diagnosis of NIDDM [ACP 92, Hendrikse 92]. According to American guidelines, the annual cycle may start four years later, provided the first examination establishes the absence of DR beyond any doubt.

The figures 14.1 to 14.6 in section 14.3 may legitimate the American as well as the Dutch guidelines. During the first years after the onset of NIDDM, the incidence rates of vision threatening retinal disorders are rather insignificant. Consequently, the American guidelines hardly expose patients to hazard, if NIDDM is diagnosed shortly after

the actual onset. The tighter Dutch guidelines are preferable in case NIDDM is not diagnosed until some years after the actual onset. Recent findings in Australia and the United States indicate, that the onset of NIDDM may occur nine to twelve years before the clinical diagnosis [Harris 92].

19.4 Conclusion of the Chapter

Some general observations conclude this chapter. Section 19.2 outlines arguments that plead for providing IDDM patients with ophthalmic care according to scenario three or four. These arguments are not intended to impose a certain policy. They merely want to relate the outcomes of the prognosis to evidence that may support policy decisions.

Section 19.1 has explained why it is far too early to present conclusive statements on the reliability of the prognosis. However, it is quite legitimate to compare the results with outcomes of other investigations. A cohort simulation by Fendrick, Javitt and Chiang [92] followed 750 patients for sixty years from the onset of IDDM. The population closely corresponds to the annual incidence of IDDM in Sweden. Qua technique, the Swedish simulation is congenial to the previously presented simulations by Javitt and associates for the United States. Therefore, the marginal notes in section 4.3 also apply to the Swedish simulation. At an annual discount rate of 0%, it concludes that annual ophthalmic examinations enable the patients to realise 3,168 years vision gain, provided they all strictly comply with screening guidelines. This result corresponds to 84,480 years vision gain in a cohort with 10,000 female and 10,000 male IDDM patients. However, the cumulative prevalence of blindness in the absence of ophthalmic care equals 44,629 years in the present simulation (table 11.2, section 11.3). This is hardly more than half the total vision gain in the Swedish simulation. It is not surprising that the maximum vision gain in this simulation is roughly a quarter of the gain realised in the Swedish simulation. *Mutatis mutandis*, the same observations apply to the prognosis of IDDM patients. This study leads to findings which are far more conservative than the outcomes of the Swedish simulation.

We may also compare this simulation with the one by Dasbach and co-workers [91]. In their cohort simulation for 1,000 IDDM patients, 388 sight years were gained (=7,760 sight years for 20,000 patients) at a discount rate of 5% over a period of sixty years. In this group, 52% had eye tests once a year, 26% once every two years and 22% never. In the present simulation, this would imply that 52% of the patients follow scenario four, 26% scenario three and 22% scenario zero, provided no patient initially suffers from DR. At a discount rate of 5%, the IDDM simulation points to 4,568 years

realised sight gain and 2,765 years prevented vision loss for this group of patients (cf. table 11.11, section 11.6). The IDDM simulation is therefore more conservative than the simulation by Dasbach and associates. However, its outcomes are much closer to Dasbach's than to Fendrick's simulation.

Dasbach and associates also present results of NIDDM simulations. Among 1,000 insulin taking patients who developed NIDDM on average at the age of fifty years, the sight gain equalled 59.5 years (=1,190 sight years for 20,000 patients) over a period of sixty years at a discount rate of 5%. Among these patients, 44% had an ophthalmic examination once a year, 16% once every two years and 40% never. For NIDDM-a patients who develop NIDDM-a at the age of fifty-five years, the present simulation points to 706 years realised sight gain and 416 years prevented vision loss at the same discount rate and the same scenario distribution (table 14.11, section 14.6). Far less sight years were gained in Dasbach's simulation for NIDDM-b patients: 19.7 years (=394 years for 20,000 patients). The corresponding totals in the present NIDDM-b simulation are 798 and 385 years. In other words, one might conclude that Dasbach's NIDDM simulations broadly supports the present NIDDM simulation.

Furthermore, shifts in the ethnic composition of the Dutch population cause uncertainty. Investigations in the United States have revealed, that incidence rates of DM differ considerably in various ethnic groups [Paisey 84a, 84b; Haffner 88, 90, 91; Nelson 89; Stern 91; Bransome 92]. Among Blacks, Hispanics and native Americans, the relative risk is respectively 1.8, 3.1 and 10.8 times as large as among Whites. At present, persons of Arabic origin constitute the most important group of Dutch immigration flows[3]. The prevalence of DM equalled 4.6% among 2,150 inhabitants of Saudi Arabia, nearly half of whom were younger than fifteen years [Abu-Zeid 92]. An earlier investigation in Saudi Arabia revealed a prevalence rate of 4.3% among 5,222 inhabitants [Fatani 87]. These rates are considerably higher than in the Netherlands: 1.88% in 1993 (cf. section 18.2). According to a Australian study of women born in Arabic countries, the prevalence rate of gestational DM equalled 7.2% as compared to 5.2% among women born in northern Europe [Beischer 91].

In Algeria, the prevalence of IDDM among children younger than fifteen years is lower than in the Netherlands: 0.027% versus 0.070% [Bessaoud 90]. The latter rate is de-

3 Most immigrants are Moroccan or Turkish by origin. It was impossible to find statistics on the incidence and prevalence of DM in Morocco and Turkey. Therefore, the statistics borrowed from studies in Algeria, Australia, France, Saudi Arabia and Sudan may be considered as approximations.

termined by prognosis results that were omitted in the previous chapter. According to the same study for Algeria, the incidence rate rose from 0.0016% to 0.0081% between 1981 and 1988. In Sudan, the incidence rate for the same age group has also risen considerably, namely from 0.0059% in 1987 to 0.0101% in 1990 [Elamin 92]. The latter rate comes near to the incidence rates for France and Italy. These outcomes harmonise with the decrease in incidence rates of IDDM from northern to southern Europe [Vaandrager 84; Beaufort 88]. In contrast, persons of Arabian origin face significantly higher NIDDM prevalence rates. Recent findings by the *World Health Organisation* confirm this dissimilarity [King 93]. The second of these two opposed occurrences has by far the greatest impact, not the least because there may be more than ten NIDDM patients for every IDDM patient in 2020. Therefore, immigration will probably stimulate the prevalence of NIDDM. Moreover, a study by Hours and associates [84] in the French *département du Rhône* reveals that the prevalence of IDDM among children from Algerian, Moroccan and Tunisian origin is over twice as high as among French autochthonic children: 0.0102% versus 0.0042%.

Beside immigrants from Arabian countries, the Netherlands counts many citizens of Hindustan origin. In West Yorkshire (United Kingdom) and in South India, the prevalence of IDDM was respectively 0.036% and 0.026% among Indian children aged fifteen years or younger [Bodansky 87; Ramachandran 92]. Therefore, Indian children seem to be at lower risk of IDDM than Dutch children. The opposite applies to older persons. The age-adjusted prevalence of NIDDM among Indian immigrants in Northwest London was nearly ten times as high as among Whites [Cruickshank 91]. An investigation in Coventry (United Kingdom) revealed similar outcomes, although the differences were less striking [Simmons 92]. Consequently, Hindustan immigrants are similar to Arabic immigrants regarding epidemiologic aspects of DM. They will probably contribute to increases in the occurrence of DR. This progression may be offset by the fact that immigrants are on average younger than the autochthonic population. It may take several decades, before this difference has disappeared. However, so far there are no publications on the effect of immigration on the prevalence of DM in the Netherlands. Therefore, the prognosis leaves immigration out of consideration.

Despite this uncertainty, table 18.9 in section 18.5 makes it clear that the demand for ophthalmic care among diabetic patients will rise considerably until 2020. For screening and photocoagulation of DR, 23% to 33% more ophthalmologists are required, 5% to 22% extra ophthalmic assistants and 24% to 39% additional secretarial staff members. As these predictions have a conservative nature, they rather underestimate than overestimate the actual increase in the demand for ophthalmic care. The scenarios two and three, which seem justifiable on the basis of this investigation, require respectively

forty-three and sixty-two additional full-time ophthalmologists in 2020 as appears from table 18.9. The ageing of the general population may erect important barricades, so that it seems quite unlikely that this demand will be met during the next decades. According to the medium variant of the *Population Forecasts*, the proportion of persons older than 64 years will increase from 12.96% in 1993 to 13.87% in 2005 and to 18.14% in 2020 [CBS 91b; 92c]. Consequently, the general population will inevitably demand considerably more ophthalmic care [Morse 86; 87]. The present shortage of eighty ophthalmologists on a total of 385 will approximately quadruple in 2005 according to estimates by the *Dutch Academy of Ophthalmology* [NOG 92:vii]. Although this publication does not present predictions for subsequent years, the sizeable growth in the number of the older persons will probably make the shortage of ophthalmologists even more acute between 2005 and 2020.

The demarcation of this study provides no room for finding solutions to these problems. However, this by no means diminishes the importance of the outcomes. They forewarn that persistently and rapidly growing shortages in the supply of ophthalmic care require substantial policy adjustments at short notice. In the absence of radical measures, many diabetic patients, beside numerous other patients, will be in imminent danger of blindness that could have been prevented rather easily, painlessly and economically by existing ophthalmic techniques. Is this justifiable in a country that pretends to offer its citizens high-quality health care?

F

Conclusions

20

Summary and Conclusions

20.1 Introduction

Within twenty years after the onset of diabetes mellitus (DM), the prevalence of diabetic retinopathy (DR) reaches the following maxima: 98% for IDDM patients (age of onset <30 years); 95% and 72% for insulin taking and not-insulin taking NIDDM patients (age of onset ≥30 years). At first, DR damages the functioning of the retina only in some eyes perceptibly, but after some years it seriously threatens the vision of numerous eyes. Ultimately, 14% to 35% of the diabetic patients become visually impaired and 6% to 12% blind. In the United States, DR is the most important cause of blindness for ages between twenty and seventy-four years. So far, no medical therapies have proved to be effective against DM or DR. According to newspaper-reports, some results of the *Diabetes Control and Complications Trial* will be published shortly. They are said to demonstrate unambiguously, that strict metabolic control significantly reduces the likelihood of complications like DR among IDDM patients.

In the earlier half of the eighties, clinical investigations have indisputably established, that timely laser treatments prevent, or significantly delay, the occurrence of poor eyesight and blindness in more than half the treated eyes. Patients usually perceive the first symptoms of DR long after the moment when the condition of retina enables laser treatments to reach their highest effectiveness. It is then quite probable that only surgery may preserve a limited fraction of the eyesight. Therefore, diabetic patients should receive frequent ophthalmic examinations, so that indications for laser treatments can be diagnosed timely. This obviously raises the question how frequently patients should be screened. How much blindness and poor eyesight can various scenarios of ophthalmic care prevent? Which resources do these scenarios require regarding personnel, matériel and finances? Which savings in production losses and facilities provided for disabilities do they realise?

20.2 Methods

Following clinical traditions, it may seem self-evident to examine these questions by clinical investigations. However, since the effectiveness of laser treatment has been definitely demonstrated, ethical aspects provide an insurmountable barrier to experimental studies. They should include a control group, but it is unacceptable to withhold treatment that is definitely effective. Furthermore, rigorous experimental investigations of chronic disorders, like DM and DR, require data covering several years, so that they cannot answer these questions in the short term. *Case-control* studies fail to offer an adequate alternative, because there is a lack of sufficient evidence for retrospective investigations, as laser treatments were not applied on a large scale until recently.

Several investigators use computer simulations to answer these questions. This technique does not raise ethical objections, when it confronts large cohorts of diabetic patients with different scenarios of ophthalmic care. However, existing simulations on DR have serious drawbacks. They distinguish a limited number of states to imitate the disease progression by discrete Markov processes. Therefore, they are unable to relate the effectiveness of laser treatments to the severity of DR, nor can they associate the sensitivity and the specificity of ophthalmoscopy with the condition of the retina. As ophthalmoscopy and photocoagulation are the principal medical actions in such simulations, this raises doubts about the reliability of the results.

These limitations demand a more sophisticated approach. Therefore, a new, and possibly unique, simulation technique was developed. It requires just a small set of findings on the prevalence of retinal and visual disorders to simulate the disease progression in cohorts of any size, where several aspects of each individual eye are followed nearly stepwise from the onset of DM until death. Although this approach avoids the principal shortcomings of other simulations on DR, it also has limitations. It needs, for instance, evidence that epidemiologic and clinical investigations have not revealed so far. The sensitivity and specificity of ophthalmic examinations may illustrate this point. The probability of an erroneous diagnosis increases, as the retinal condition approaches the limit value of two neighbouring diagnostic categories. In other words, the sensitivity and specificity of ophthalmoscopy vary as a function of the retinal condition. Nevertheless, the available evidence only presents average values on the quality of eye examinations. This forces the simulation to use assumptions. If future evidence makes up these deficiencies, the model may accommodate those new findings. Another limitation of the model concerns the valuation of the retinal condition. Medical science usually employs real numbers between zero and one to symbolise the condition of the

body or an organ. One might wonder, however, whether that condition can be represented in one dimension. This fundamental problem would require a separate investigation.

The economic evaluation comprises (1) direct costs of ophthalmic care determined at charges for the Netherlands in 1992, (2) effects measured in sight gain and (3) benefits which consist of savings in facilities provided for disabilities and in production losses at prices for 1990 and 1992. Because costs, effects and benefits do not progress synchronously, they are discounted at the same discount rate. The analysis uses three discount rates: 0%, 5% and 10%. Production losses are determined by the *human capital approach* and the *friction costs technique*. The second produces considerably lower estimates than the first.

The simulation borrows prevalence findings from well-known epidemiologic investigations. They are relatively more unanimous on retinal than on visual disorders. In case of doubt, the simulation opts for a conservative approach so as to avoid overestimating the effectiveness of ophthalmic care in combating blindness and poor eyesight. At the end of 1991, the principally concerned medical associations in the Netherlands reached agreement on guidelines regarding the screening, diagnosis and treatment of DR. Although the simulation follows these guidelines, it distinguishes option α and option β, because there still exists division of opinion on fluorescein angiography. The first option indicates the majority view that advocates a higher frequency, whereas the second represents supporters of a lower frequency. Consequently, option α faces higher direct costs and less auspicious cost-effectiveness ratios. In accordance with the conservative nature of this simulation, table 20.1 presents results based on option α.

20.3 IDDM: Insulin-Dependent Diabetes Mellitus

In table 20.1, the first column, holding results, relates to insulin-dependent diabetic patients, whose age of onset equals fifteen years according to model assumptions. At that age, the life expectation of female and male diabetic patients equals on average nearly forty-four years, which corresponds to 71% of the life expectation in the general population of over sixty-two years (cf. table 11.1, section 11.2). Every patient is on average 2.23 years blind in the absence of ophthalmic care (scenario zero). If all patients strictly follow scenario two or three, the prevalence of blindness decreases by 39% or 47% respectively. Table 8.1 in section 8.4 presents details on these scenarios. The agreement mentioned in the previous paragraph resembles scenario three to a considerable extent.

		Age of onset			
		15 years	35 years	55 years	75 years
Life expectation at onset (years)	s0..s4	43.96	33.40	19.61	8.20
Blindness duration (years/patient)	s0	2.23	0.81	0.34	0.08
Blindness prevention (years/patient)	s2	0.87	0.12	0.05	0.00
	s3	1.05	0.19	0.07	0.01
Blindness prevention (% of s0)	s2	38.78%	15.26%	13.95%	5.67%
	s3	46.98%	24.12%	20.85%	12.45%
Direct costs per year vision gain (*) (**)	s2	*f* 7,919	*f* 21,978	*f* 35,014	*f* 84,607
	s3	*f* 8,787	*f* 21,873	*f* 34,302	*f* 178,112
Direct costs minus benefits per year vision gain					
- Human capital approach (*) (**)	s2	-*f* 67,298	-*f* 16,444	-*f* 92	*f* 48,784
	s3	-*f* 64,922	-*f* 14,882	*f* 2,334	*f* 96,473
- Friction costs technique (*) (**)	s2	-*f* 2,502	*f* 15,269	*f* 28,758	*f* 79,370
	s3	-*f* 1,593	*f* 15,336	*f* 28,382	*f* 164,778

All outcomes: averages for female and male patients
Age of onset ≥35 years: averages for insulin taking and not-insulin taking patients
s0, s2, s3, s4: scenario 0, 2, 3, 4; compliance 100%
(*) Direct costs, effects and benefits discounted at 5% per year
(**) Age of onset 75 years: averages of 3 findings *f* Dutch guilder

Table 20.1 - Principal findings of IDDM and NIDDM simulations; option α [1]

The direct costs per year sight gain equal nearly *f* 7,900 or *f* 8,800 respectively. If savings in production losses are determined by the *human capital approach*, the benefits surpass the costs by *f* 67,000 or *f* 65,000 respectively per year sight gain. This balance decreases to *f* 2,500 or *f* 1,600 respectively, if the estimates are based on the *friction costs technique*. The savings in facilities provided for disabilities compensate 89% or 80% respectively of the direct costs (cf. table 12.1, section 12.3). In other words, the outcomes of this rather conservative simulation may financially justify the provision of ophthalmic care to IDDM patients following scenario two or three.

1 Beside the calculation of life expectation, the scenarios one and four are left out of consideration for the following reasons. Among the four scenarios offering eye care, scenario one is at farthest from the recommended guidelines in the Netherlands and the United States. In scenario four, cost-effectiveness ratios are far less auspicious than in scenario three.

Beside the results presented in table 20.1, the progression in the quantity of ophthalmic actions is worthy of mention. The number of ophthalmic examinations grows proportionally to the intensity of care, whereas the number of fluorescein angiograms and laser treatments remains rather stable in the four scenarios with ophthalmic care: s1, s2, s3, s4 (cf. tables 11.4 to 11.8, section 11.4). For instance, the quantity of panretinal laser treatments, which presents the highest growth rate, increases by 39% from scenario one to scenario four, while eye care intensifies by 700%. In brief, more intensive ophthalmic care for IDDM patients makes the centre of gravity in ophthalmic activities shift from photocoagulation to ophthalmoscopy.

According to the legend of table 20.1, all patients strictly comply with the scenario guidelines. As this hypothesis conflicts with facts, it seems detrimental to the meaning of the outcomes. However, precisely because of strict compliance, a *mélange* of various scenarios can easily be constituted to approach the observed compliance. This method enables the application of the simulation results to situations where quite different degrees of compliance prevail (cf. section 8.8).

20.4 NIDDM: Not-Insulin-Dependent Diabetes Mellitus

From an epidemiologic perspective, the duration of DM is the principal determinant in the progression of DR. This implies, that the total damage caused by DR depends on the total number of years in which patients are exposed to DM during their life-times. Therefore, NIDDM patients constitute a relatively more heterogeneous group than IDDM patients. This explains why the simulation distinguishes three ages of onset for NIDDM. The last three columns of table 20.1 present some key results. Patients who develop NIDDM at the age of 35 years face DM for 33.40 years on average, whereas the average duration equals 8.20 years for the age of onset of 75 years. This difference reflects the reduction in life expectation by ageing. Meanwhile, the relative gap in life expectation as compared to the general population narrows from 22% to 17% between the ages of onset of 35 and 75 years (cf. table 14.1, section 14.2). The cumulative prevalence of blindness among NIDDM patients is considerably lower than among IDDM patients. Striking differences exist within the group of NIDDM patients. While disregarding blindness caused by other disorders, the youngest-onset patients are on average 0.81 years blind and the oldest-onset patients 0.08 years. The outcomes reveal, that ophthalmic care prevents relatively more blindness as patients have to face NIDDM for more years: in scenario three 24.12% in the youngest-onset group versus 12.45% in the oldest-onset group.

Subsequent to the preceding observations, it is self-evident that the effectiveness of ophthalmic care decreases and that cost-effectiveness ratios fall, as the age of onset increases. The direct costs per year sight gain equal nearly *f* 22,000 for patients who develop NIDDM at the age of 35 years. According to the *human capital approach*, the benefits considerably exceed the direct costs, but the *friction costs technique* points to the opposite conclusion. Consequently, for these patients policy decisions on ophthalmic care cannot only be based on financial arguments. Regarding patients who develop NIDDM at the age of 55 years, the direct costs per year sight gain equal some *f* 35.000. According to the *human capital approach*, the benefits almost equal the direct costs, but there is an unfavourable difference of over *f* 28,000 following the *friction costs technique*. At the oldest age of onset, the cost-effectiveness ratios are even less favourable. For these patients, curing other disorders may take precedence of DR.

For NIDDM patients, quantities of ophthalmic actions also progress remarkably. The number of eye examinations increases nearly proportionally to the intensity of ophthalmic care, but the quantities of fluorescein angiograms and laser treatments have considerably lower growth rates (cf. tables 14.5 to 14.8, section 14.4). The largest discrepancy concerns laser treatments for the youngest-onset patients. For older ages of onset, the differences are substantially smaller. As ophthalmic care for NIDDM patients is intensified, relatively more eye examinations and relatively less laser treatments should be performed. However, this shift is less pronounced than for IDDM patients. Table 20.1 is based on full compliance. Observations on this subject in the previous section also apply to NIDDM patients.

20.5 Prognosis

The prognosis, which covers the period 1993-2020, rests on three pillars: (1) population forecasts until the year 2050 by the *Netherlands' Central Bureau of Statistics (CBS)*, (2) currently available incidence rates for DM and (3) results of the IDDM and NIDDM simulations that the sections 20.3 and 20.4 refer to. Each of the three variants in the CBS population forecasts have traversed the entire prognosis model. The low and the high variant yield results that diverge only marginally from the outcomes of the medium variant (deviation of total prevalence in 2020: IDDM ≤4.0%; NIDDM ≤3.0%). Therefore, this section only presents the latter.

The size of the general population increases by 11%, whereas the group younger than thirty years decreases by 5%. The number of IDDM patients remains nearly constant until 2020, but the age composition changes because of ageing. Consequently, the

average duration of IDDM rises and the number of blind patients grows by 12% in the absence of ophthalmic care (cf. table 19.1, section 19.2; figure 18.11, section 18.3). In scenario zero, over 5% of the IDDM patients are blind in 2020 (cf. table 18.1, section 18.2; table 18.3, section 18.3). According to table 20.2, ophthalmic care reduces the number of blind patients by 36% and 45% in scenario two and three respectively. The direct costs equal *f* 113 to *f* 147 per patient per year. According to the *friction costs technique* the benefits surpass the direct costs by *f* 106 to *f* 110 per patient per year. Again, financial considerations may provide sufficient ground to justify ophthalmic care for IDDM patients following scenario two or three.

		IDDM	NIDDM
Total number of patients		35638	369652
Average age (years)		40.00	67.66
Prevalence of blindness	s0	1854	5055
(total number of patients)	s2	1179	4422
	s3	1022	4057
Blindness prevention (% of s0)	s2	36.44%	12.52%
	s3	44.90%	19.73%
Direct costs per patient per year	s2	*f* 113	*f* 60
	s3	*f* 147	*f* 83
Direct costs minus benefits per patient per year			
- Human capital approach	s2	-*f* 1,946	*f* 0
	s3	-*f* 2,210	-*f* 4
- Friction costs technique	s2	-*f* 106	*f* 52
	s3	-*f* 110	*f* 71
s0, s2, s3: scenario 0, 2, 3			
Compliance: 100%		*f* Dutch guilder	

Table 20.2 - Principal findings of IDDM and NIDDM prognoses for 2020; medium variant

Between 1993 and 2020, the general population in the Netherlands of thirty years and older grows by 23%, while its average age rises. This involves, for instance, an increase by 55% of the group older than 64 years. In 2020, the number of NIDDM patients is expected to be 47% larger than in 1993 (cf. table 18.2, section 18.2), but the average duration of NIDDM will nearly remain constant (cf. table 19.2, section 19.3). If no ophthalmic care were provided, approximately 45% more NIDDM patients would be blind in 2020 than in 1993 (cf. figure 18.12, section 18.3) and they would consti-

tute some 1% of the total NIDDM population (cf. table 18.2, section 18.2; table 18.3, section 18.3). According to table 20.2, the prevalence of blindness decreases by 13% and 20% in the scenarios two and three respectively. The direct costs per patient per year sight gain are lower than for IDDM patients, namely *f* 60 and *f* 83. However, the direct costs surpass the benefits according to the *friction costs technique*. Following the observations in the previous section, one might consider to give precedence to the younger-onset NIDDM patients in the detection of DR. The older-onset patients are likely to require the same ophthalmic care as the general population, because at older ages cataract, glaucoma and senile macular degeneration threaten the vision of diabetic patients more than DR.

In scenario two and three, the fight against DR requires 30% more ophthalmologists in 2020 than in 1993 (cf. table 18.9, section 18.5). If the present number of ophthalmologists were to remain constant until 2020, scenario three would then necessitate to allocate 16% of the available capacity to DR. Meanwhile, the general population will also claim far more ophthalmic care, not the least because the number of inhabitants older than 64 years is expected to grow by 55%. It seems unavoidable, that the present shortage of ophthalmologists continues to rise during the next decades. Consequently, many patients are in imminent danger of avoidable blindness and poor vision, unless ophthalmic care receives means to embark on a new course.

20.6 Suggestions for Further Research

The following questions advance prospective research subjects. Some concern bottlenecks that emerged in this investigation, while others endeavour to elaborate the technique which was developed for this simulation or to discover new applications for it.

1. As ophthalmic care for IDDM and 35-year onset NIDDM patients is intensified, the quantity of laser treatments rises rather insignificantly. Consequently, the centre of gravity in ophthalmic activities shifts towards ophthalmoscopy. Can other diagnostic techniques facilitate attenuating bottlenecks of ophthalmic care in the short run?

2. Can the simulation technique that was developed for this study adequately support cost-effectiveness analyses of other complications caused by DM?

3. Is this technique qualified for serving cost-effectiveness analyses of other chronic diseases?

4. How does the prevalence of blindness and poor vision relate to the duration of NIDDM and its age of onset in the absence of ophthalmic care?

5. Can the condition of the retina, or an element of the retina, be adequately expressed in a one-dimensional unit of measurement?

6. How does the state of retina affect the sensitivity and specificity of (a) ophthalmoscopy, (b) stereoscopic colour fundus photography of seven standard fields and (c) fundus photography of one field through pharmacologically dilated and undilated pupils?

7. What relationship does exist between the condition of the retina and the effectiveness of different types of photocoagulation during a patient's life-time after treatment?

8. How do costs of facilities provided for visual disabilities relate to visual acuity, or changes therein?

9. What is the relation between visual acuity and labour productivity for some major economic activities?

10. Are the risk ratios of diabetic retinopathy, glaucoma and cataract for older diabetic patients correlated with one another?

11. In this simulation, the construction of logistic-normal probability density functions is based on the prevalence of two severity levels of DR. Can this technique also be applied to three or more grades of severity?

12. In these simulations, sorting patient records requires the larger half of processing time for cohorts comprising 10,000 patients. The execution time of the well-known recursive procedure *"Quick Sort"* decreased by 25% to 50% after alterations in the algorithm. Are further reductions possible?

G

Summary in Dutch

21

Samenvatting

21.1 Inleiding

Binnen twintig jaar na het ontstaan van diabetes mellitus (DM) bereikt de prevalentie van diabetische retinopathie (DR) de volgende maxima: 98% voor IDDM-patiënten (leeftijd bij diagnose <30 jaar); 95% en 72% voor insuline-gebruikende en niet-insuline-gebruikende NIDDM-patiënten (leeftijd bij diagnose ≥30 jaar). Aanvankelijk doet DR slechts in enkele ogen merkbaar afbreuk aan de functie van het netvlies. Maar na enige jaren neemt de ernst van de aandoening toe, zodat uiteindelijk 14% à 35% van de patiënten slechtziend wordt en 6% à 12% blind. In de Verenigde Staten vormt DR de belangrijkste oorzaak van blindheid voor leeftijden van 20 tot en met 74 jaar. Er bestaan tot dusverre nog geen therapieën waarvan vaststaat, dat ze het ontstaan van DM en DR doeltreffend tegengaan. Wel wordt volgens voorlopige berichten binnenkort voor IDDM-patiënten het wetenschappelijke bewijs geleverd, dat een goede metabole instelling de kans op complicaties, waaronder DR, significant verkleint.

Klinische onderzoeken in de eerste helft van de jaren tachtig hebben onomstotelijk aangetoond, dat tijdige laserbehandelingen het optreden van blindheid en slechtziendheid in ruim de helft van de behandelde ogen voorkomen, dan wel significant vertragen. Het blijkt echter, dat patiënten zelf pas symptomen van DR beginnen waar te nemen lang na het moment waarop laserbehandelingen de hoogste effectiviteit hebben. Dan bieden doorgaans alleen chirurgische ingrepen nog een bescheiden kans om de visus in beperkte mate te behouden. Diabetes-patiënten dienen daarom regelmatig oogcontroles te ondergaan, zodat de noodzaak van laserbehandelingen op tijd kan worden vastgesteld. Dit roept vanzelfsprekend de vraag op met welke frequentie deze controles moeten geschieden. Hoeveel blindheid en slechtziendheid kunnen uiteenlopende scenario's van oogzorg voorkomen? Welke personele, materiële en financiële inzet vragen deze scenario's? En welke besparingen op produktieverliezen en invaliditeitsvoorzieningen maken ze mogelijk?

21.2 Methode

Vanuit een klinische traditie ligt het voor de hand langs klinische weg antwoorden te zoeken op deze vragen. Sinds de doeltreffendheid van laserbehandelingen definitief is aangetoond vormen ethische aspecten echter een onoverkomelijke barrière voor een dergelijke studie. Experimenteel onderzoek vereist namelijk een controlegroep. Maar het is onaanvaardbaar patiënten therapieën te onthouden die aantoonbaar effectief zijn. Verder vraagt een gedegen experimentele studie vele jaren vanwege het chronische karakter van DM en DR, zodat ze de genoemde vragen niet op korte termijn kunnen beantwoorden. Een *case-control* onderzoek vormt geen geschikt alternatief. Voor een dergelijke retrospectieve studie bestaat namelijk onvoldoende materiaal, aangezien laserbestralingen pas sinds enkele jaren op grotere schaal toepassing vinden.

Diverse auteurs gebruiken computersimulaties om de genoemde vragen te beantwoorden. Met deze techniek is het bijvoorbeeld mogelijk grote cohorten patiënten zonder ethische bezwaren in korte tijd uiteenlopende scenario's van oogzorg te laten doorlopen. Bestaande simulaties op het terrein van DR blijken echter belangrijke beperkingen te hebben. Ze onderscheiden slechts een gering aantal stadia om het ziekteverloop volgens Markov-processen na te bootsen. Daarom kunnen ze geen verband leggen tussen de ernst van DR en de effectiviteit van laserbestralingen. Evenmin kunnen ze de specificiteit en de sensitiviteit van oogspiegelingen afhankelijk stellen van de staat van het netvlies. Dit geeft reden tot twijfel aan de betrouwbaarheid van de uitkomsten. Oogspiegelingen en laserbehandelingen vormen immers de belangrijkste medische verrichtingen in die simulaties.

Deze beperkingen scheppen behoefte aan een meer verfijnde benadering. Voor deze studie werd daarom een simulatietechniek ontwikkeld die, voor zover bekend, uniek is. Op basis van een kleine verzameling gegevens inzake de prevalentie van netvlies- en visusstoornissen kan ze het ziekteverloop per oog vanaf het ontstaan van DM tot de dood gedetailleerd volgen. Zo verdwijnen weliswaar de eerder genoemde beperkingen, maar toch kent ook deze methode schaduwzijden. Ze vereist namelijk gegevens waarover epidemiologische en klinische onderzoeken tot dusverre nog geen uitsluitsel bieden. De sensitiviteit en specificiteit van oogspiegelingen kunnen dit illustreren. De kans op een foutieve diagnose neemt vanzelfsprekend toe, naarmate de staat van het netvlies dichter bij de grenswaarde ligt tussen twee diagnosecategorieën, zodat de sensitiviteit en de specificiteit niet constant zijn ten opzichte van de staat van het netvlies. Desalniettemin biedt het beschikbare feitenmateriaal uitsluitend gemiddelde waarden. Dat dwingt deze simulatie veronderstellingen te maken. Mocht er in de toekomst empi-

risch materiaal verschijnen dat in deze leemte voorziet, dan kan het zonder meer een plaats krijgen in het model. Een andere beperking van het model betreft de waardering van de staat van het netvlies. Gewoonlijk gebruikt de geneeskunde daartoe reële getallen tussen nul en een. Het is echter de vraag of de toestand van het hele lichaam of van een lichaamsdeel in één dimensie kan worden uitgedrukt. Dit probleem is zo fundamenteel, dat het binnen het beperkte kader van deze studie geen plaats kan krijgen.

De economische evaluatie omvat (1) directe kosten van oogzorg uitgedrukt in Nederlandse tarieven voor 1992, (2) effecten gemeten in visuswinst en (3) baten bestaande uit besparingen op invaliditeitsvoorzieningen en verminderingen van produktieverliezen gerekend tegen gegevens voor 1990 en 1992. Aangezien kosten, effecten en baten geen synchrone ontwikkeling kennen, worden ze tegen dezelfde discontovoet verdisconteerd. De analyse hanteert de volgende discontovoeten: 0%, 5% en 10%. Produktieverliezen worden geschat met de *human capital approach* en de *frictiekostentechniek*. De tweede komt tot beduidend lagere ramingen dan de eerste.

De simulatie ontleent prevalentiecijfers aan bekende epidemiologische onderzoeken. Voor netvliesaandoeningen blijken deze studies verhoudingsgewijs eenstemmiger dan voor visusstoornissen. In geval van twijfel kiest de simulatie een behoudende benadering om te voorkomen, dat de effectiviteit van oogzorg bij de bestrijding van blindheid en slechtziendheid wordt overschat. Voor de diagnose, screening en behandeling van DR volgt de simulatie de consensus die eind 1991 in Nederland werd bereikt. Maar omdat er nog verdeeldheid bestaat over fluorescentie-angiografie, onderscheidt de simulatie de varianten α en β. De eerste vertegenwoordigt het meerderheidsstandpunt dat een hogere frequentie bepleit, terwijl de tweede recht wil doen aan voorstanders van een lagere frequentie. Daarom kent variant α meer directe kosten en minder gunstige kosten-effectiviteitsratio's. Aansluitend bij de genoemde behoudende benadering, presenteert tabel 21.1 resultaten op basis van variant α.

21.3 IDDM: Insulin-Dependent Diabetes Mellitus

In deze tabel heeft de eerste kolom met resultaten betrekking op insuline-afhankelijke patiënten. Volgens modelveronderstellingen ontstaat IDDM bij het bereiken van de leeftijd van 15 jaar. Op dat moment bedraagt de gemiddelde levensverwachting voor mannelijke en vrouwelijke patiënten bijna 44 jaar, zijnde 71% van de levensverwachting van ruim 62 jaar voor de algemene bevolking (cf. tabel 11.1, § 11.2). Elke patiënt ondervindt gemiddeld 2,23 jaar blindheid bij afwezigheid van oogzorg (scenario 0). Ontvangen alle patiënten oogzorg volgens de scenario's twee of drie, dan

blijkt het mogelijk de prevalentie van blindheid met respectievelijk 39% of 47% terug te dringen. Tabel 8.1 (§ 8.4) geeft nadere bijzonderheden omtrent deze scenario's. De sinds 1991 in Nederland bestaande consensus over de frequentie van oogheelkundig onderzoek voor diabetes-patiënten kent veel overeenkomst met scenario drie.

		Leeftijd van incidentie			
		15 jaar	35 jaar	55 jaar	75 jaar
Levensverwachting bij incidentie (jr)	s0..s4	43,96	33,40	19,61	8,20
Duur blindheid (jaren per patiënt)	s0	2,23	0,81	0,34	0,08
Preventie blindheid (jaren per patiënt)	s2	0,87	0,12	0,05	0,00
	s3	1,05	0,19	0,07	0,01
Preventie blindheid (% van s0)	s2	38,78%	15,26%	13,95%	5,67%
	s3	46,98%	24,12%	20,85%	12,45%
Directe kosten / jaar visuswinst (*) (**)	s2	*f* 7.919	*f* 21.978	*f* 35.014	*f* 84.607
	s3	*f* 8.787	*f* 21.873	*f* 34.302	*f* 178.112
Directe kosten minus baten per jaar visuswinst					
- Human capital approach (*) (**)	s2	-*f* 67.298	-*f* 16.444	-*f* 92	*f* 48.784
	s3	-*f* 64.922	-*f* 14.882	*f* 2.334	*f* 96.473
- Frictiekosten-techniek (*) (**)	s2	-*f* 2.502	*f* 15.269	*f* 28.758	*f* 79.370
	s3	-*f* 1.593	*f* 15.336	*f* 28.382	*f* 164.778

Alle resultaten: gemiddelden voor mannelijke en vrouwelijke patiënten
Leeftijd incidentie ≥35 jaar: gemiddelden voor insuline-gebruikende en overige patiënten
s0, s2, s3, s4: scenario 0, 2, 3, 4; alle patiënten leven scenariorichtlijnen strikt na
(*) Directe kosten, effecten en baten verdisconteerd à 5% per jaar
(**) Leeftijd van incidentie 75 jaar: gemiddelden van 3 bevindingen

Tabel 21.1 - Resultaten van IDDM- en NIDDM-simulaties; variant α [1]

De directe kosten per jaar visuswinst bedragen bij benadering respectievelijk *f* 7.900 of *f* 8.800. Worden verminderingen van produktieverliezen geschat volgens de *human capital approach*, dan blijkt er per jaar visuswinst een batig saldo te ontstaan

1 De scenario's één en vier blijven buiten beschouwing, behalve bij de bepaling van de levensverwachting. Dit heeft de volgende redenen. Van de vier scenario's met oogzorg kent scenario één de grootste discrepantie met de richtlijnen waarover thans in Nederland en in de Verenigde Staten consensus bestaat. In scenario vier zijn de kosten-effectiviteitsratio's aanzienlijk minder gunstig dan in scenario drie.

van kosten en baten ter grootte van respectievelijk *f* 67.000 of *f* 65.000. Dat saldo daalt tot respectievelijk *f* 2.500 of *f* 1.600 bij gebruik van de *frictiekosten-techniek*. De besparingen op invaliditeitsvoorzieningen compenseren respectievelijk 89% of 80% van de directe kosten (cf. tabel 12.1, § 12.3). Kortom, zelfs op basis van deze behoudende simulatie lijkt het alleen al op financiële gronden verantwoord aan IDDM-patiënten oogzorg te verschaffen volgens scenario twee of drie.

Naast de resultaten die tabel 21.1 weergeeft, is de volume-ontwikkeling van oogheelkundige verrichtingen vermeldenswaard. Het aantal oogspiegelingen blijkt gelijke tred te houden met de zorgintensiteit, maar de aantallen fluorescentie-angiogrammen en laserbestralingen veranderen in de vier scenario's met oogzorg (s1, s2, s3, s4) slechts in beperkte mate (cf. tabellen 11.4 t/m 11.8, § 11.4). Zo blijkt het volume panretinale laser behandelingen, dat relatief de grootste groei kent, toe te nemen met 39% van scenario één naar scenario vier, terwijl de zorgintensiteit met 700% groeit. Kortom, bij intensivering van de zorg voor IDDM-patiënten verschuift het zwaartepunt van de werkzaamheden in de oogzorg van laserbestralingen naar oogspiegelingen.

Blijkens de legende bij tabel 21.1 leven alle patiënten de scenariorichtlijnen strikt na. Deze hypothese staat haaks op de feiten, hetgeen de betekenis van de resultaten lijkt te schaden. Maar juist omdat alle patiënten de voorgeschreven controle-intervallen strikt volgen, kan er gemakkelijk een melange worden gevormd van verschillende scenario's om de waargenomen compliance te benaderen. Op deze manier kunnen de uitkomsten van de simulatie in zeer uiteenlopende situaties toepassing vinden (cf. § 8.8).

21.4 NIDDM: Not-Insulin-Dependent Diabetes Mellitus

De schade die diabetes-patiënten gemiddeld genomen in hun leven van DR ondervinden, hangt nauw samen met het totale aantal jaren waarin ze aan DM lijden. Daarom vormen NIDDM-patiënten verhoudingsgewijs een meer heterogene groep dan IDDM-patiënten. Dit verklaart waarom de simulatie voor NIDDM drie leeftijden van incidentie onderscheidt. Daarvan geven de drie laatste kolommen in tabel 21.1 enkele belangrijke resultaten weer. Patiënten die op 35-jarige leeftijd NIDDM ontwikkelen, lijden gemiddeld 33,40 jaar aan DM. Ontstaat NIDDM op 75-jarige leeftijd, dan is de gemiddelde duur 8,20 jaar. Dit komt vanzelfsprekend voort uit de daling van de levensverwachting bij het toenemen van de leeftijd. Tegelijkertijd daalt de achterstand in levensverwachting ten opzichte van de algemene bevolking: 22% bij incidentie op 35-jarige leeftijd; 17% op 75-jarige leeftijd (cf. tabel 14.1, § 14.2). NIDDM-patiënten lijden aanzienlijk minder lang aan blindheid dan IDDM-patiënten. Daarnaast kent NIDDM

nog andere onderlinge verschillen. Patiënten die op 35-jarige leeftijd NIDDM ontwikkelen, zijn gemiddeld circa tienmaal zo lang blind als patiënten bij wie op 75-jarige leeftijd NIDDM ontstaat, namelijk 0,81 jaar tegenover 0,08 jaar. Blindheid ten gevolge van andere aandoeningen laat de simulatie terzijde. Uit de resultaten blijkt, dat oogzorg relatief meer blindheid weet te voorkomen bij patiënten die gemiddeld langer met NIDDM kampen: in scenario drie 24,12% bij incidentie op 35-jarige leeftijd tegenover 12,45% bij incidentie op 75-jarige leeftijd.

Na het voorgaande ligt het voor de hand, dat de effectiviteit van oogzorg vermindert en de kosten-effectiviteitsratio's verslechteren, naarmate de leeftijd van incidentie toeneemt. De directe kosten per jaar visuswinst blijken bijna *f* 22.000 te bedragen voor patiënten bij wie op 35-jarige leeftijd NIDDM ontstaat. Volgens de *human capital approach* overtreffen de baten de directe kosten nog ruimschoots, maar de *frictiekosten-techniek* leidt tot de tegenovergestelde conclusie. Bij beleidsbeslissingen kan daarom niet worden volstaan met een beschouwing van financiële aspecten. Voor patiënten die op 55-jarige leeftijd NIDDM ontwikkelen, bedragen de directe kosten per jaar visuswinst circa *f* 35.000. De *human capital approach* brengt directe kosten en baten nog betrekkelijk dicht bijeen, maar volgens de *frictiekosten-techniek* zijn de directe kosten per jaar visuswinst ruim *f* 28.000 groter dan de baten. Ontstaat NIDDM op 75-jarige leeftijd, dan zijn de kosten-effectiviteitsratio's nog ongunstiger. Het lijkt waarschijnlijk, dat de behandeling van andere aandoeningen voor deze groep een hogere prioriteit heeft.

Ook voor NIDDM-patiënten kent de oogzorg een opvallende volume-ontwikkeling. Het aantal oogspiegelingen volgt ruwweg de groei van de zorgintensiteit, terwijl de aantallen fluorescentie-angiogrammen en laserbehandelingen daar duidelijk bij achterblijven (cf. tabellen 14.5 t/m 14.8, § 14.4). De grootste discrepantie betreft laserbestralingen voor patiënten die op 35-jarige leeftijd NIDDM ontwikkelen. Bij incidentie op latere leeftijd zijn de afwijkingen kleiner. Een intensivering van de oogzorg voor NIDDM-patiënten gaat dus eveneens gepaard met een taakverschuiving van laserbestralingen naar oogspiegelingen, al zijn de veranderingen kleiner dan voor IDDM-patiënten. Tabel 21.1 veronderstelt volledige compliance. De opmerkingen die de vorige paragraaf hierover heeft gemaakt, gelden ook voor NIDDM-patiënten.

21.5 Prognose

De prognose, die de periode 1993-2020 omvat, rust op drie pijlers: (1) bevolkingsprognoses tot 2050 van het CBS, (2) thans bekende incidentiecijfers voor DM en (3)

resultaten van de hierboven besproken simulaties voor IDDM- en NIDDM-patiënten. De bevolkingsprognoses van het CBS kennen drie varianten. Bij elke variant heeft het prognosemodel volledige berekeningen uitgevoerd. De lage en de hoge variant leiden tot resultaten die hooguit enkele procenten afwijken van de uitkomsten in de midden variant (afwijking totale prevalentie in 2020: IDDM ≤4,0%; NIDDM ≤3,0%). Daarom komt nu alleen de laatste ter sprake.

		IDDM	NIDDM
Totaal aantal patiënten		35.638	369.652
Gemiddelde leeftijd (jaren)		40,00	67,66
Prevalentie van blindheid	s0	1.854	5.055
(totaal aantal patiënten)	s2	1.179	4.422
	s3	1.022	4.057
Preventie blindheid (% van s0)	s2	36,44%	12,52%
	s3	44,90%	19,73%
Directe kosten per patiënt per jaar	s2	*f* 113	*f* 60
	s3	*f* 147	*f* 83
Directe kosten minus baten per patiënt per jaar			
- Human capital approach	s2	-*f* 1.946	*f* 0
	s3	-*f* 2.210	-*f* 4
- Frictiekosten-techniek	s2	-*f* 106	*f* 52
	s3	-*f* 110	*f* 71
s0, s2, s3: scenario 0, 2, 3			
Alle patiënten leven de scenariorichtlijnen strikt na.			

Tabel 21.2 - Resultaten van IDDM- en NIDDM-prognoses voor 2020; midden variant

De algemene bevolking groeit in de beschouwde periode met 11%, terwijl de groep jongeren tot dertig jaar 5% kleiner wordt. Het aantal IDDM-patiënten blijft tot 2020 nagenoeg gelijk, maar de leeftijdsopbouw verandert door vergrijzing. Hierdoor neemt de gemiddelde duur van IDDM toe en ontstaat er circa 12% meer blindheid bij afwezigheid van oogzorg (cf. tabel 19.1, § 19.2; figuur 18.11, § 18.3). Ruim 5% van deze patiënten is in 2020 blind (cf. tabel 18.1, § 18.2; tabel 18.3, § 18.3). Blijkens tabel 21.2 dringt oogzorg het aantal blinden in de scenario's twee en drie terug met respectievelijk 36% en 45%. De directe kosten bedragen *f* 113 en *f* 147 per patiënt per jaar. Volgens de *frictiekosten-techniek* overtreffen de baten de kosten met *f* 106 en *f* 110 per patiënt per jaar (cf. tabellen 18.11 en 18.12, § 18.5). Financiële overwegingen lij-

ken dus opnieuw voldoende rechtvaardiging te bieden om aan IDDM-patiënten oogzorg te verschaffen volgens een van deze twee scenario's.

Tussen 1993 en 2020 groeit de algemene bevolking in de leeftijd van dertig jaar en ouder met 23%, terwijl deze groep bovendien vergrijst. Dit blijkt bijvoorbeeld uit de toeneming van het aantal personen ouder dan 64 jaar met 55%. Zo zal Nederland in 2020 naar verwachting 47% meer NIDDM-patiënten tellen dan in 1993 (cf. tabel 18.2, § 18.2). De gemiddelde duur van NIDDM blijft in die periode vrijwel constant (cf. tabel 19.2, § 19.3). Bij afwezigheid van oogzorg zullen er in 2020 circa 45% meer NIDDM-patiënten blind zijn dan in 1993 (cf. figuur 18.12, § 18.3). Ze vormen dan ruim 1% van het totale aantal NIDDM-patiënten (cf. tabel 18.2, § 18.2; tabel 18.3, § 18.3). Blijkens tabel 21.2 daalt de prevalentie van blindheid in de scenario's twee en drie met respectievelijk 13% en 20%. De directe kosten per patiënt per jaar zijn lager dan voor IDDM-patiënten, namelijk *f* 60 en *f* 83. Maar de directe kosten overtreffen de baten volgens de *frictiekosten-techniek*. In aansluiting bij opmerkingen uit de voorgaande paragraaf valt op grond van deze resultaten te overwegen bij de opsporing van DR voorrang te geven aan patiënten bij wie NIDDM op jongere leeftijd optreedt. Patiënten die later NIDDM ontwikkelen, vragen veeleer dezelfde oogzorg als de algemene populatie, aangezien cataract, glaucoom en seniele macula-degeneratie het gezichtsvermogen van diabetes-patiënten op oudere leeftijd meer blijken te schaden dan DR.

In de scenario's twee en drie vraagt de bestrijding van DR in 2020 30% meer oogartsencapaciteit dan in 1993 (cf. tabel 18.9, § 18.5). Gerekend naar het huidige aantal oogartsen moet dan in scenario drie 16% van de capaciteit voor DR worden bestemd. Eerder werd al opgemerkt, dat het aantal personen ouder dan 64 jaar terzelfder tijd met 55% groeit. Bijgevolg neemt zowel in de algemene bevolking als onder diabetespatiënten de behoefte aan oogzorg aanzienlijk toe. Het huidige tekort aan oogartsen zal zodoende in de komende decennia waarschijnlijk sterk stijgen, zodat veel patiënten bij ongewijzigd beleid onnodig blind of slechtziend dreigen te geraken.

Appendix

Appendix 1

Abbreviations

The symbol * represents a reference to a term in the glossary (appendix 2).

AAO	American Academy of Ophthalmology
ADA	American Diabetes Association
ADR	annual discount rate*
BR	background retinopathy* (= DR excluding both ME and PDR) ($BR = DR \cap [\neg ME \cup \neg PDR]$)
CBS	Netherlands Central Bureau of Statistics
DCCT(RS)	Diabetes Control and Complications Trial (Research Group)
DERIMSG	Diabetes Epidemiology Research International Mortality Study Group
DM	diabetes mellitus*
DR	diabetic retinopathy* (including ME and PDR)
DRS(RG)	Diabetic Retinopathy Study (Research Group)
DRVS(RG)	Diabetic Retinopathy Vitrectomy Study (Research Group)
DVN	Diabetes Vereniging Nederland (Netherlands Diabetes Association)
ETDRS(RG)	Early Treatment Diabetic Retinopathy Study (Research Group)
f	Dutch guilder (exchange rate September 14th, 1993: *f* 1.00 = US $ 0.5531 or US $ 1.00 = *f* 1.8080)
FA	fluorescein angiography* / fluorescein angiogram
HbA_{1c}*	haemoglobin A_{1c}
IDDM*	insulin-dependent diabetes mellitus
IGF-I	insulin-like growth factor I*
μ (or: μm)	micron (10^{-6} metre)
ME	macular edema* ($ME \subset DR$)
MPSG	Macular Photocoagulation Study Group
N	set of non-negative integers or natural numbers {0, 1, 2, 3, ...}

NIDDM	non-insulin-dependent diabetes mellitus (NIDDM = NIDDM-a ∪ NIDDM-b)
NIDDM-a*	non-insulin-dependent diabetes mellitus (insulin taking)
NIDDM-b*	non-insulin-dependent diabetes mellitus (not-insulin taking)
NOG	Nederlands Oogheelkundig Gezelschap (Netherlands Academy of Ophthalmology)
Option α / β	screening option with higher / lower frequencies of fluorescein angiography (cf. table 8.5, section 8.8)
PDR	proliferative diabetic retinopathy* (PDR $\subset$ DR)
QALYs	quality-adjusted life-years
$\mathbf{R}$	set of real numbers
RAM	random access memory in computers
s0, s1, s2, s3, s4	scenario 0, 1, 2, 3, 4 (cf. table 8.1, section 8.4)
STG	Stuurgroep Toekomstscenario's Gezondheidszorg (Netherlands Steering Committee on Future Health Scenarios)
TPPV	trans pars plana vitrectomy*
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
$\mathbf{Z}$	set of integers $\{0, 1, -1, 2, -2, 3, -3, \ldots\}$
$\mathbf{Z}^+$	set of positive integers $\{1, 2, 3, \ldots\}$

Appendix 2

Glossary

The symbol * represents a cross-reference. Several explanations are borrowed from textbooks on computer science, economics, epidemiology, medicine, operations research or statistics.

Absorbing state	discrete state* which is never left after it is entered
Acidosis	abnormally high acidity in the blood and body fluids
Aetiology	science of the causes of disease
Albuminuria	excessive secretion of albumen (=one of a group of proteins*) as a result of renal failure (cf. proteinuria*)
Algorithm	finite sequence of effective statements that, when applied to a problem, will solve it
Allocation (of resources)	distribution of factors of production among the various uses to which they might be put
Argon laser treatment	photocoagulation* by argon laser (80% of energy: between 488 and 514.5 nm wave length) [Schepens 81:26]
Array	arrangement of data in computer storage such as a row of data or data columns and rows (cf. static memory* allocation)
Average analysis	analysis of average costs, effects and / or benefits
β-cells	cells in islets of Langerhans* of the pancreas* which synthesise and secrete insulin* in response to changes in the metabolic state of the organism (cf. metabolism*)
Background retinopathy (BR)	all grades of diabetic retinopathy* excluding both macular edema* and proliferative diabetic retinopathy*
Blindness	definition in this study: cf. section 7.3
Boolean	data type* which can assume either of the logical values *True* or *False*
C-peptide	metabolically inactive polypeptide chain connecting proinsulin and insulin*, produced by the pancreatic β-cells* in equimolar amounts with insulin as a result of proinsulin cleavage

Capillary	minute thin-walled blood vessel
Case-control study	backward study design to compare a group of cases and one or more groups of non-cases selected from available cases and non-cases
Cataract	opacity of the lens
Chebyshev polynomial	polynomial* of degree n: $T_n(x) = \cos(n \arccos x)$ [Press 89:165]
Coefficient of determination (R^2)	square of correlation coefficient; measure of goodness of fit; proportion of the variation in the dependent variable explained by the model
Cohort study	study design in which information on the study factor is known for all subjects at the beginning of the follow-up period; the population at risk* is followed for a given period through re-examinations or population surveillance
Cost-analysis	analysis of costs (of a medical technique)
Cost-benefit analysis	cost-analysis* of different (medical) techniques; effects are stated in money terms; results are expressed in the balance of costs and benefits
Cost-effectiveness analysis	cost-analysis* of alternative (medical) techniques having differential success in achieving the same outcome; results are expressed in terms of costs per unit of outcome
Cost-minimisation analysis	cost-analysis* of alternative (medical) techniques having equivalent effects
Cost-utility analysis	cost-analysis* of different (medical) techniques; effects are determined in utility* units; results are expressed in terms of costs per utility unit
Cotton wool spots	microinfarcts of the retinal* tissue
Cross-sectional study	study involving one set of observations at one hypothetical point of time
Cumulative incidence	the number of newly detected cases that developed during follow-up divided by the number of disease-free subjects at the start of follow-up
Data structure	(computer science) abstract way of representing data that is independent of a particular computer implementation
Data type	(computer science) formal description of the set of values that a variable can have (examples: boolean*, character, integer, string, real)
Diabetes control	action taken to achieve glucose homeostasis, i.e. to avoid hyperglycaemia* and hypoglycaemia* caused by diabetes mellitus* or the treatment of diabetes mellitus (diet, oral treatment*, insulin*)

Diabetes mellitus (DM)	chronic disorder of carbohydrate metabolism* due to a disturbance of the normal insulin* mechanism, characterised by hyperglycaemia*, glycosuria*, and alterations of protein* and fat metabolism*, producing polyuria*, polydipsia*, weight loss, ketosis*, acidosis*, and coma
Diabetes mellitus type I	inflammatory destruction of β-cells* in the pancreas* leading to essentially complete loss of the ability to synthesise and release insulin* (incidence* rates reach peak at younger ages); cf. section 2.3
Diabetes mellitus type II	results from insulin resistance* of the body and diminished insulin secretion* (incidence* rates are positively correlated to ageing); cf. section 2.3
Diabetic retinopathy (DR)	retinal* manifestation of diabetes mellitus* characterised by microaneurysms*, small punctate haemorrhages, yellowish exudates*, and neovascularisation*; saccular (=in small sacs) dilatation of retinal veins may also occur and massive haemorrhages into the vitreous* may result in blindness*
Diffuse macular edema	diabetic macular edema* with diffuse leakage characterised by (1) diffuse edema*, (2) systemic factors (cardiac and renal fluid retention, severe hypertension, pregnancy) and (3) cystoid macular edema following panretinal laser treatment* [Bresnick 86]
Direct benefits	(medical technology assessment) savings in direct costs*
Direct costs	(medical technology assessment) costs of medical action plus treatment costs borne by patients related to disease, screening or treatment
Disc diameter	1,500µm
Discount rate	rate of interest used in discounting*
Discounting	process of determining the present value* of a stream of later payments, receipts or effects
Discrete state	category which contains a range of states
Doubling of visual angle*	halving of maximum distance at which an eye can distinguish a specific object
Dynamic variable	variable having a data structure* that may expand or contract during execution of a computer programme
Échelle de Monnoyer	chart for ordinal measurement of visual acuity* comprising eleven values: 0 (no vision) , 0.1, 0.2, ... 1 (normal vision); respective type sizes on visual acuity chart: --, 50, 25, 16.6, ..., 5.55, 5
Edema	serum leakage through the incompetent walls of the retinal blood vessels, particularly those in the macular* area
Endothelium	layer of cells lining blood vessels

Erythrocyte	red blood cell
Experimental study	study in which one group of subjects is given a treatment and another group a placebo; subjects are allocated to both groups by randomisation (simplest type of experimental study)
Externalities	effects, either good or bad, on parties not directly involved in the production or use of a commodity
Exudate	material with a high content of protein* and cells, that has passed through the walls of vessels into adjacent tissues or spaces, especially in inflammation
Exudative diabetic retinopathy	diabetic macular edema* with focal leakage; characterised by (1) exudate* rings, (2) multifocal edema* and (3) perifoveolar edema and exudate [Bresnick 86]
Fibrin	white insoluble protein* precipitated as a tangle of threads when blood clots
File	collection of information of arbitrary size which is regarded as an entity by its users
Fluorescein-angiography (FA)	rapid injections of a solution of sodium fluorescein into the antecubital vein and recording the results photographically at intervals of 0.6 to 0.8 seconds [L'Esperance 90:675]
Focal laser treatment	50µm to 100µm diameter laser burns at ≥300µm from the centre of the macula* [Frank 86:959]
Fourier transformation	development of a complex periodic function into a series of sine and cosine functions
Friction costs technique	(medical technology assessment) estimate of lost production or earnings during friction period* as a consequence of disease or disablement
Friction period	(medical technology assessment) period needed to replace a sick or disabled worker
Fundus	internal bottom surface of a hollow organ
Fundus photography	photography of retina*
Funduscopy	see: ophthalmoscopy (alternative orthography: fundusscopy)
Generation preference rate	factor representing the weight of the interests of future generations
Gestational diabetes mellitus	onset of glucose intolerance during pregnancy
Glaucoma	abnormally high level of intraocular pressure
Glycosuria	presence of sugar in the urine
Goodness of fit	see: coefficient of determination

Grid laser treatment	50µm to 200µm spots, spaced one burn diameter apart, in "grid" pattern surrounding the centre of the macula* except on its nasal side [Frank 86:959]
Haemoglobin	iron-containing reddish protein* occurring in erythrocytes*
Handle	indirect pointer to a dynamic variable* allowing heap* compacting
Hard exudate	white or yellowish, shiny, and sharply defined exudate* without surrounding pigmentation [L'Esperance 90:669]
Hazard rate (discrete)	rate of failure (death) in period t conditional upon survival to the start of period t
HbA_{1c}	haemoglobin* A_{1c}
Heap	computer memory used to store dynamic variables*
Human capital approach	(medical technology assessment) estimate of potentially lost production or earnings as a consequence of disease or disablement
Hyperglycaemia	excess of glucose in the blood; fasting value ≥6.7 mmol/litre or ≥11.1 mmol/litre two hours after 75 gram oral glucose load under standardised conditions (World Health Organisation diabetes mellitus* criteria 1985) [STG 91:202]
Hypoglycaemia	shortage of glucose in the blood; fasting value <2.5 mmol/litre [Veneman 92]
Hypoxia	oxygen want or deficiency; any state wherein a physiologically inadequate amount of oxygen is available to, or utilised by, tissue without respect to cause of degree
IDDM	insulin*-dependent diabetes mellitus* (in this study: age of onset <30 years); cf. section 2.3
Incidence	number of new cases of a given disease per unit of time
Indirect benefits	(medical technology assessment) savings in indirect costs*
Indirect costs	(medical technology assessment) all costs related to disease, screening or treatment apart from direct costs*
Inflation	rise in the average level of prices; increase in the money supply
Insulin	hormone produced in islets of Langerhans* that maintains the glucose level in the blood
Insulin resistance	lessened insulin* sensitivity of the body
Insulin secretion	output of insulin* by β-cells*
Insulin-like growth factor (IGF-I)	small polypeptides (=units in the structure of proteins* grouped into a molecular chain) structurally similar to A-chain of insulin* [Frank 86:955]
Interest rate	price paid per monetary unit borrowed (usually: per year)
Interviewer bias	distortion in estimates of effects resulting from the manner in which subjects are interviewed

Ishemia	blood deficiency in part of the body
Islets of Langerhans	discrete clusters of endocrine cells scattered throughout the pancreas*
Iteration	repeated execution of (computer programme) statements
Ketosis	presence of an excess of ketones, like acetone, in systems
Kolmogorov-Smirnov-test	nonparametric test to investigate whether two independent samples have been drawn from the same population or from populations with the same distribution
Labour productivity	(value of) output produced per unit of time worked
Laser treatment	see: photocoagulation
Life expectation	expected number of years remaining in the life of a person at some specific age
Logarithmic interval scale	(ophthalmology) chart for interval measurement of visual acuity*; (possible implementation: $^{10}\log \alpha$, where α is reciprocal of the outcome of Snellen-chart* measurement
Logit	cf. formula 7.8 in section 7.4
Longitudinal study	study involving at least two sets of observations or ongoing surveillance of the study population over a given follow-up period
Lymphocyte	leukocyte (=white blood cell) inhabiting both the blood and the lymph
Macrovascular complications	complications related to larger blood vessels
Macula (lutea)	yellow spot of the retina* comprising the fovea centralis, the parafovea and the perifovea (Ø 5,500µm)
Macular edema* (ME)	retinal thickening at or within 500µm of the centre of the macula*; and/or hard exudates* at or within 500µm of the centre of the macula, if associated with thickening of adjacent retina* and/or a zone or zones of retinal thickening one disc area in size at least part of which was within one disc diameter* of the centre [ETDRSRG 91a:742]
Marginal analysis	analysis of marginal costs*, effects* and / or benefits*
Marginal benefits	increase in the total benefits per additional unit of input
Marginal costs	increase in the total costs per additional unit of outcome / effect
Marginal effects	increase in the total effects per additional unit of input
Markov process (discrete state)	series of dependent trials constituting a process of discrete states* in which the transition from one state to another is a fixed probability not affected by the past history of the system
Metabolic control	management of blood glucose level

Metabolism	process in organism or single cell by which nutritive material is built up into living matter or protoplasm (=semifluid semitransparent substance of complex organic compounds) is broken down into simpler substances
Microaneurysm	slight dilation of the capillaries*
Microvascular complications	complications related to capillaries*
Module	(computer programming:) a unit of a computer programme which allows independent development
Monte Carlo technique	random statistical sampling used to obtain approximations of the solution of certain problems by trial and error
National product	sum of all values-added* in a nation's economy
Neovascularisation	development of new vessel systems
Nephropathy	any of the several diseases of the kidneys
Neuropathy	any of the several diseases of the neural system
NIDDM-a	non-insulin* dependent diabetes mellitus*; insulin* taking (in this study: age of onset ≥30 years); cf. section 2.3
NIDDM-b	non-insulin* dependent diabetes mellitus*; not-insulin* taking (in this study: age of onset ≥30 years); cf. section 2.3
Nominal interest rate	interest rate* (as opposed to real interest rate*)
Ophthalmoscopy	ophthalmic examination
Opportunity costs	value of the foregone benefits of the next best alternative
Oral treatment of DM	tablets taken by mouth to accomplish metabolic control*
P-value	the smallest level of significance for which the observations lead to rejection of the null hypothesis
Pancreas	gland near stomach secreting digestive juices and insulin*
Panretinal laser treatment	hundreds of closely spaced photocoagulation* burns around the mid-peripheral retina* [Frank 86:957]
Pascal	(computer programming) structured computer language using modules* and allowing for many different data types*
Pathogenesis	origin or development of a disease
Pearson χ^2–test	nonparametric test to investigate the degree of contingency between the observed and the expected number of observations in various categories
Peripheral (retina)	retina* apart from macula lutea*
Photocoagulation	therapy involving the channelling of a light beam, usually from a laser source, to the retina* of the eye through the dilated pupil; as the light strikes the retina it is absorbed and transformed into energy forming a coagulated mass

Polydipsia	excessive thirst
Polynomial	cf. formula 7.1 in section 7.2
Polyuria	passage of an excessive quantity of urine
Present value	value *"now"* of sum(s) payable at later date(s); the value *"now"* of a (stream of) later effect(s) (cf. footnote 2, section 4.4)
Prevalence	number of known cases of a given disease at a given moment
Price index	measure of the average prices of commodities; its weights are based on the spending pattern of a typical household (consumer price index)
Primary prevention	designed to prevent the onset of a disease
Probability density function	description of the distribution of probability for a continuous random variable
Proliferative diabetic retinopathy (high risk) (PDR)	new vessels on or within 1 disc diameter* of the optic disc (NVD) ≥ standard photograph 10A (about 1/4 to 1/3 disc area), with or without vitreous* or preretinal haemorrhage*; or vitreous and /or preretinal haemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere ≥ 1.4 disc area [ETDRSRG 91a:742]
Protein	any of a class of complex combinations of amino acids which are essential constituents of all living cells
Proteinuria	excessive urinary secretion of proteins* (cf. albuminuria*)
Quality of life	state of well-being consisting of three components: physical, mental and social functioning [STG 91:25]
Random number generator	module* in a computer programme that draws at least one random number from a specific distribution at each call
Real discount rate	discount rate* corrected for changes in the purchasing power of money
Real interest rate	interest rate* corrected for changes in the purchasing power of money
Recall bias	distortion in estimates of effects resulting from the manner in which subjects recall past events
Record	(computer science) data structure* which is a collection of fields or attributes of a specific entity in a table of a relational database
Recursion	ability of a module* (in a computer programme) to call itself
Relative life expectation*	life expectation* in a specific group at some age divided by the life expectation of the general population at the same age
Retina	part of the eye that receives the light and converts it into chemical energy; in this manuscript occasionally: shorthand term for peripheral retina*

Risk	probability of a disease-free individual's developing a given disease over a specific period conditional on that individual's not dying from any other disease during the period
Risk factor	factor associated with the development of a disease / complication [STG 91:25]
Scatter laser treatment	= panretinal laser treatment*
Secondary prevention	designed to detect a disease at an early stage before it gives rise to symptoms
Selection bias	distortion in estimates of effects resulting from the manner in which subjects are selected for study population
Self blood glucose monitoring techniques	techniques applied by the patient (or family members, etc.) to achieve metabolic control*
Sensitivity	proportion of those with the condition who have a positive test
Sensitivity analysis	analysis of the results of tests or trials of values to determine the response, interdependence, etc., of the values; comparison of change(s) in output to change(s) in input
Seven-field fundus photography*	identification of retinal lesions by grading stereoscopic colour fundus* photographs of seven 30° fields of the posterior retina* [Klein 85b:118]
Simulation model	formal representation of a process to represent one system by another
Snellen-chart	chart for ordinal measurement of visual acuity*; possible outcomes: 20/20 (normal vision), 20/25, ... 20/800 (e.g. 20/40 means: able to read letters at ≤20 yards which are readable at ≤40 yards with normal visual acuity)
Soft exudate	larger than hard exudates*, up to a half-disc diameter* in size, with blurred and indistinct edges [L'Esperance 90:669]
Specificity	proportion of those without the condition who have a negative test
Standard error (σ)	square root of variance which is estimated by dividing the sum of squares due to error by $(N - 2)$
Standard normal distribution	any x drawn from the set of real numbers meets the following equation: $$P(x < X) = \int_{-\infty}^{X} \frac{1}{\sqrt{2\pi}} e^{-0.5\,y^2} dy \quad \{x, X, y \in \mathbf{R}\}$$
Static memory	set of fixed locations with a fixed size in computer memory that are reserved for some specific variables as long as a module* or a programme is active

Stochastic process	system using random numbers to determine progression
Survival analysis	analysis of data to determine the length of time that elapses before death occurs
Tertiary prevention	designed to prevent complications and increases in the severity of complications
Trans pars plana vitrectomy (TPPV)	ophthalmic surgery - usually three-port - to manipulate vitreoretinal surface relationships and to remove blood and fibrin* from vitreous* cavity
Transient state	discrete state* which can be left after it is entered
Uniform distribution [0, 1)	(continuous) any x drawn from the interval of real numbers [0, 1) meets the following equation: $P(x < X) = X$ $\{x, X \in \mathbf{R} \mid 0 \leq x < 1; 0 < X \leq 1\}$ (discrete; usual implementation in binary digital computers) the probability of obtaining any random number α equals $1/2^n$ $\{\alpha = k / 2^n \mid k \in 0, 1, 2, \ldots, 2^n - 1; n \in Z^+\}$
Utility	(medical technology assessment) satisfaction resulting from a specific health state
Value added	value of a firm's output minus the value of the inputs purchased from other firms
Viscosity	quality of a fluid that causes it to resist flow
Visual acuity	acuteness of visual perception which might be measured by (1) échelle de Monnoyer*; (2) Snellen-chart*; (3) Logarithmic interval scale*
Visual angle	formed at the retina* by rays from the extremities of an object viewed
Visual impairment	visual acuity* ≤ 6/12 (20/40) in better eye: able to read letters at ≤6 metres (≈20 feet) which are readable at ≤12 metres (≈40 feet) with normal visual acuity
Vitreous	transparent jelly-like tissue filling ball of eye
What-if analysis	see: sensitivity analysis*
Withdrawal	loss of study subjects because of migration, lack of participation and death
Xenon arc treatment	photocoagulation* by xenon arc (wave length: 350 to 1,000 nm) [Schepens 81:20]

Appendix 3

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comment: In the main text, bibliographic references omit elements like *et al.* and the first two digits of years. Numbers preceded by a colon indicate page numbers. The names of advisory boards, research groups and organisations are abbreviated.

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Appendix 4

Sorting

Regarding simulations for IDDM and NIDDM patients, figure 8.8 (section 8.6) illustrates how the module *Disease Progression* assigns values to patient records in order to quantify the progression of DR and visual acuity in every eye. At three points, the diagram indicates that an array should be sorted: array A twice and array B once. Following figure 7.8 in section 7.6, the number of lines in both arrays equals the number of living patients. For the left as well as for the right eye, the three sorting actions are accomplished four times: for the macula, the peripheral retina, central acuity and peripheral vision. Each period therefore requires twenty-four of these sorting actions. For cohorts holding 10,000 female or 10,000 male patients, sorting initially took some 60% to 70% of the total processing time notwithstanding the use of *Quick Sort*, which generally offers significantly faster processing than other well-known sorting algorithms. A recursive and an iterative version of this algorithm were tried [recursive: Wirth 76:79; iterative: Press 89:265-6]. Considering the sizeable share of sorting in the total processing time, it seemed worthwhile to pay extra attention to this matter. Subsequent paragraphs briefly indicate how sorting was studied and what results this investigation produced.

After consulting literature on computer programming, the following algorithms seemed the most promising: *Shell Sort*, *Heap Sort* and *Quick Sort*. *Shell Sort* may be regarded as a more sophisticated variant on *Straight Insertion*, which is an elementary sorting algorithm suitable for smaller arrays. *Heap Sort* is a rather fast technique that requires no additional memory. *"... Quick Sort is, on most machines, on average, for large* N *the fastest known sorting algorithm"* [Press 89:264]. Its recursive version demands supplementary storage for the stack[1], the size of which is rather unpredictable. It depends on the number of data elements, their values and the structure of the array. If

1 In this data structure, elements are added and removed from only one end. It is a LIFO structure (last in, first out).

memory is tight, *Quick Sort*[2] may cause a stack/heap collision leading to memory overflow after a series of successful executions of the same module with the same equipment. Two variants of these three algorithms were studied: one by Wirth and another one by Press et al.

Testing was performed on an *Apple Macintosh SE/30* (*Motorola* MC68030, 15.6672 MHz plus MC68882, RAM-cache 256 Kb) by a programme compiled in *Think Pascal 3.0 (Symantec Corporation)* while all debug options were set to maximise speed[3]. The sorting modules processed arrays containing elements of the data type *Real* (floating-point notation; 32 bits; range: $\pm 1.5 \times 10^{-45}$ to $\pm 3.4 \times 10^{38}$). The first two columns of table A4.1 indicate that the performance of each algorithm was tested by six trials. In the first trial, an array of sixteen elements was sorted 1,024 times, in the second an array of 256 elements 64 times, and so forth. Each trial involved sorting 16,384 ($=2^{14}$) elements. The six trials were accomplished for (a) ordered arrays, (b) random arrays and (c) inversely ordered arrays. Table A4.1 mentions the total sorting times per trial in seconds. The algorithm *Shell Sort* (version Wirth), for instance, needs 0.88 seconds to sort an ordered array with sixteen elements 1,024 times. The results reveal that sorting a random or an inversely ordered array demands more time than an ordered array.

Table A4.2 summarises the results of table A4.1. Every number in the columns (a), (b) and (c) equals the unweighted average of the six related execution times in table A4.1. The first number in column (a), for instance, corresponds to the average of the six execution times mentioned in table A4.1 for sorting ordered arrays by Wirth's *Shell Sort*. Each number in the last column of table A4.2 equals the unweighted average of the corresponding results in the columns (a), (b) and (c). *Heap Sort* is, on average, clearly faster than *Shell Sort*. *Quick Sort* allows shorter execution times than *Heap Sort*, apart from the disappointing performance of Press's iterative module as to inversely ordered arrays. Consequently, the previously cited statement by Press et al. on *Quick Sort* does not seem to conflict with the outcomes of these trials, not the least because table A4.1 indicates that *Quick Sort* increases its lead over the other algorithms, as the number of elements per array grows.

2 *Quick Sort* was invented by C.A.R. Hoare.

3 The same algorithms were implemented in *Borland's Turbo Pascal 5.5* on an *MS-DOS* computer with a 25 MHz *80386 Intel* processor plus *80387 math co-processor*. Ceteris paribus, they require on average 150% more processing time than the *Think Pascal* implementation on the *Apple Macintosh SE/30*.

elements	trials	(a) Ordered		(b) Random		(c) Inversely Ordered	
		Wirth Shell	Press Shell	Wirth Shell	Press Shell	Wirth Shell	Press Shell
16	1024	0.88	0.93	1.18	1.30	1.15	1.38
64	256	0.65	0.77	1.35	1.78	1.45	1.47
256	64	0.73	1.10	2.62	3.05	3.40	2.08
1024	16	0.73	1.45	6.93	5.45	11.28	2.72
4096	4	0.75	1.80	23.83	11.58	42.67	3.33
16384	1	0.75	2.15	87.52	18.03	167.92	3.97
		Wirth Heap	Press Heap	Wirth Heap	Press Heap	Wirth Heap	Press Heap
16	1024	1.65	1.27	1.62	1.20	1.47	1.08
64	256	2.03	1.57	1.98	1.52	1.80	1.35
256	64	2.87	2.33	2.75	2.22	2.55	2.03
1024	16	3.65	3.05	3.50	2.92	3.30	2.73
4096	4	4.45	3.78	4.27	3.65	4.12	3.47
16384	1	5.23	4.50	5.07	4.37	4.85	4.17
		Wirth RecQS	Press IterQS	Wirth RecQS	Press IterQS	Wirth RecQS	Press IterQS
16	1024	1.33	0.75	1.47	0.93	1.37	0.93
64	256	1.20	0.62	1.42	0.87	1.23	1.25
256	64	1.50	0.90	1.77	1.15	1.55	3.85
1024	16	1.72	1.13	2.17	1.57	1.78	13.68
4096	4	2.00	1.42	2.50	1.85	2.03	52.75
16384	1	2.23	1.65	2.88	2.33	2.30	208.72
		Modified QS	Crijns IterQS	Modified QS	Crijns IterQS	Modified QS	Crijns IterQS
16	1024	0.55	0.57	0.85	0.88	0.60	0.62
64	256	0.48	0.50	0.97	0.98	0.52	0.55
256	64	0.73	0.73	1.35	1.35	0.80	0.82
1024	16	1.00	1.00	1.63	1.63	1.08	1.08
4096	4	1.27	1.28	2.03	2.03	1.32	1.32
16384	1	1.53	1.53	2.35	2.35	1.58	1.60

Table A4.1 - Total execution times of eight sorting programmes (in seconds)

		Ordered (a)	Random (b)	Inversely Ordered (c)	Average (a) ... (c)
Wirth Shell Sort	[Wirth 76:70]	0.75	20.57	37.98	19.77
Press Shell Sort	[Press 89:257]	1.37	6.87	2.49	3.57
Wirth Heap Sort	[Wirth 76:75]	3.31	3.20	3.02	3.18
Press Heap Sort	[Press 89:259-61]	2.75	2.65	2.47	2.62
Wirth Recursive Quick Sort	[Wirth 76:79]	1.66	2.04	1.71	1.80
Press Iterative Quick Sort	[Press 89:265-6]	1.08	1.45	46.86	16.46
Modified Quick Sort	(cf. text)	0.93	1.53	0.98	1.15
Crijns Iterative Quick Sort	(cf. text)	0.94	1.54	1.00	1.16

Table A4.2 - Average total execution times of eight sorting programmes (in seconds)

The last of the four horizontal blocks in table A4.1 and the two final lines in table A4.2 concern algorithms developed by the author on the basis of existing sorting algorithms.

According to the last column in table A4.2, *Modified Quick Sort* reduces the execution time of Wirth's recursive *Quick Sort*, the fastest algorithm found in literature on computer programming, by some 36%. *Modified Quick Sort* consists of (α) *Recursive Quick Sort* (version Wirth) and (β) *Straight Insertion Sort* [Press 89:255-6]. The main module α is applied to (partial) arrays comprising at least twelve elements, whereas module β processes smaller (partial) arrays. Testing revealed that the limit value *twelve* minimises the execution time for the previously specified computer system. Other computer equipment may realise the highest execution speed at another limit value. The following programme lines globally indicate the structure of this algorithm. The simulation uses this algorithm for all sorting operations. Consequently, the share of sorting time in total execution time dropped from 60%-70% to 49%-55%, for IDDM and NIDDM simulations respectively. Because of the recursive nature of module α, module β is also called frequently, when *Modified Quick Sort* processes larger arrays. This explains why *Modified Quick Sort* enables to save processing time, even when it is applied to larger arrays.

```
1.  procedure ModifiedQuickSort(Left, Right: Integer);
2.    var i, j : Integer; (*** other declarations ***)
3.  begin
4.    (*** Partition statements [cf. Wirth 76:79] ***)
5.    if j > Left + 10    then  ModifiedQuickSort(Left, j)
6.                        else  if j > Left    then  StraightInsertion(Left, j);
7.    if Right > i + 10   then  ModifiedQuickSort(i, Right)
8.                        else  if Right > i   then  StraightInsertion(i, Right);
9.  end; {ModifiedQuickSort}
```

The last line in table A4.2 indicates the results regarding the algorithm *Iterative Quick Sort*, which manifests a more substantial contribution by the author as compared to *Modified Quick Sort*. The iterative algorithm is almost as fast as the newly developed recursive one, although it requires no additional memory. The following Pascal procedure illustrates how this algorithm may be coded. It needs to be called only once to sort the first E elements of the globally declared array A. The procedure includes *Straight Insertion Sort* three times (lines 7-15, 21-29, 45-53), so that further procedure calls are avoided and processing speed may be optimised. The lines 7-15 manage the processing of array A for smaller values of E, whereas the lines 21-29 handle "recursive" calls by *Quick Sort* to segments of array A that comprise less than C+2 elements. Finally, the lines 45-53 are activated, when the "stack" pointer P refers to the last element of array S. This may happen in exceptional situations. Then, a run-time error would occur, if the lines 45-53 were absent. In other words, this procedure offers quite a remarkable

execution speed as well as the advantages of sorting modules that require a fixed number of additional memory addresses. The lines 34 to 42 present "pure" *Quick Sort* statements.

```
 1.  procedure CrijnsIterativeQuickSort (E, C: Integer);
       {C: limit value for switching between Quick Sort and Straight Insertion Sort}
 2.    label   97, 98, 99;
 3.    const   Size = 50;          {size of array S, which represents the "stack"}
                   {The size of array S may be adapted to specific circumstances.}
 4.    var     S : array[1..Size] of LongInt;
               i, J, L, P, R : LongInt;  K, X, Y : Real;
 5.  begin
 6.    if E <= C then
 7.      for J := 2 to E do begin
 8.        K := A[J];
 9.        for i := J - 1 downto 1 do begin
10.          if A[i] <= K then goto 97;
11.          A[i + 1] := A[i]
12.        end;  {i := J - 1 downto 1}
13.        i := 0;
14.  97:    A[i + 1] := K
15.      end  {J := 2 to E}
16.    else begin
17.      S[1] := 1;  S[2] := E;  P := 2;
18.      while P > 1 do begin
19.        while S[P] > S[P - 1] do
20.          if S[P] <= S[P - 1] + C then begin
21.            for J := S[P - 1] + 1 to S[P] do begin
22.              K := A[J];
23.              for i := J - 1 downto S[P - 1] do begin
24.                if A[i] <= K then goto 98;
25.                A[i + 1] := A[i]
26.              end;  {J - 1 downto S[P - 1]}
27.              i := S[P - 1] - 1;
28.  98:          A[i + 1] := K
29.            end;  {S[P - 1] + 1 to S[P]}
30.            S[P] := S[P - 1]
31.          end  {S[P] <= S[P - 1] + C}
```

```
32.             else begin
33.               if P < Size then begin
34.                 L := S[P - 1];  R := S[P];  X := A[(L + R) div 2];
35.                 while L <= R do begin
36.                   while A[L] < X do L := L + 1;
37.                   while X < A[R] do R := R - 1;
38.                   if L <= R then begin
39.                     Y := A[L]; A[L] := A[R]; A[R] := Y; L := L + 1; R := R - 1
40.                   end  {L <= R}
41.                 end;  {L <= R}
42.                 S[P + 1] := S[P];  S[P] := L;  P := P + 1
43.               end  {P < Size}
44.               else begin
45.                 for J := S[P - 1] + 1 to S[P] do begin
46.                   K := A[J];
47.                   for i := J - 1 downto S[P - 1] do begin
48.                     if A[i] <= K then goto 99;
49.                     A[i + 1] := A[i]
50.                   end;  {J - 1 downto S[P - 1]}
51.                   i := S[P - 1] - 1;
52.   99:             A[i + 1] := K
53.                 end;  {S[P - 1] + 1 to S[P]}
54.                 P := P - 1;  S[P] := S[P] - 1
55.               end  {else}
56.             end;  {S[P] <= S[P - 1] + C}
57.             P := P - 1;  S[P] := S[P] - 1
58.         end  {P > 1}
59.       end  {E <= C}
60.   end;  {CrijnsIterativeQuickSort}
```

Appendix 5

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