The course of diabetic retinopathy during treatment with continuous subcutaneous insulin infusion

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PROEFSCHRIFT

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CONTENTS

INTRODUCTION

This thesis tries to answer whether normoglycemia in type I diabetic patients, as it is now possible to achieve and maintain by means of continuous subcutaneous insulin infusion (CSII), can arrest or reverse the progression of diabetic retinopathy.

The question is highly relevant because diabetic retinopathy has become one of the three most frequent causes of blindness in the Netherlands and probably it is still increasing. The number of blind through diabetic retinopathy in this country is estimated to be some 4000, most of them between 45 and 60 years old (Doesschate ten 1982).

The question is not easy to answer since diabetes is a complex multifactorial disease and the microvascular disorders which underlie the retinopathy are probably of multifactorial origin including a genetic susceptibility (Frank 1984).

In the past strong evidence has accumulated to suggest that diabetic retinopathy is initiated as a result of insulin deficiency and that keeping blood glucose as close as possible to the nondiabetic range may delay or inhibit the progression of the microvascular complications (Tchobroutsky 1978).

With the usual methods of treatment however - diet and daily insulin injections - blood glucose levels may show large excursions and normoglycemia is thus difficult to maintain. A much better tool to achieve and maintain long-term normalization of blood glucose levels in ambulant type I diabetic patients is CSII, complemented by self-monitoring of blood glucose. CSII is an open-loop infusion system and supplies insulin continuously during 24 hours (Pickup et al. 1978).

Initial reports concerning the influence of CSII treatment on established diabetic retinopathy were conflicting (White et al. 1981; Puklin et al. 1982).

CSII was introduced in the Department of Clinical Endocrinology of the University of Groningen (Dr. E. van Ballegooie) in 1980. All patients who were thus treated up to 1985 contributed to this study. The influence of CSII on the course of diabetic retinopathy was studied in 3 groups of patients and the results are presented in the main part of this thesis, the chapters 3 to 5. The first group (35 patients) comprises those who were followed for one year after initiation of treatment (chapter 3). The second group (24 patients) was observed for a period of 2-5 years in order to study the long-term influence of treatment (chapter 4). In the third group (35 patients) the course of diabetic retinopathy was studied during pregnancy (chapter 5).

Chapter 1 provides a review of literature concerning diabetic retinopathy and CSII. In chapter 2 the methods of investigation are described.

CHAPTER 1

LITERATURE REVIEW

1.1. **Natural history of diabetic retinopathy**

1.1.1. *Descriptive studies*

The main structural changes in the pathologic process of diabetic retinopathy occur at the level of the retinal capillaries, small arterioles and venules. Histologically, the earliest abnormalities seen are thickening of the capillary basement membrane (Bloodworth et al. 1965; Ashton 1974) and pericyte dropout (Yanoff 1969). In the normal retinal capillary bed there is one pericyte per endothelial cell. In diabetics the pericytes die off, resulting in an increased endothelial cell to pericyte ratio. These changes in the retinal capillaries lead to an abnormal retinal vascular permeability. Under normal circumstances the tight junctions between the capillary endothelial cells create an effective blood-retinal barrier, preventing almost completely, leakage into the vitreous (Shakib et al. 1966; Cunha-Vaz et al. 1975; Waltman et al. 1978).

By means of fluorescein angiography, which method contributed enormously to the understanding of capillary microangiopathy, the leakage can be exactly localized. Moreover three other lesions involving the retinal capillaries show up by angiography, namely capillary obstruction, capillary dilatation and capillary microaneurysms.

Capillary obstruction is usually seen in the early stages of diabetic retinopathy (Ashton 1963). It is very often associated with dilatation of adjacent capillaries. Histologically, these capillaries show endothelial proliferation while the nonperfused capillaries appear as acellular strands (Bresnick et al. 1976).

Microaneurysms develop, adjacent to areas of capillary nonperfusion. They are the earliest ophthalmoscopically visible lesions but they are more easily recognized by fluorescein angiography. Microaneurysms start as thin saccular dilatations from the wall of a capillary. They gradually become occluded due to a thickening of their wall, possibly by the accumulation of basement membrane material (Bresnick et al. 1977). They are then no longer perfused and do no longer show up leakage in angiograms.

Leakage from dilated capillaries and microaneurysms results in retinal edema and the formation of hard exudates (Davis 1968). Retinal edema involving the macula is the most important cause of visual impairment in diabetic patients. Hard exudates are collections of serum lipoprotein and glial-neuronal breakdown products. Sometimes they are deposited in a circinate fashion, surrounding the leaky elements.

Vascular occlusion not only occurs in the capillaries, the precapillary arterioles may become occluded too. The obstruction of a precapillary arteriole causes in its distribution area an ischemic infarction of the inner retinal layers. This is ophthalmoscopically visible during the acute phase of the obstruction by the presence of soft exudates. These soft exudates are aggregations of swollen ends of ruptured axons in the nerve fiber layer (Madson et al. 1974). They generally disappear within several weeks to months. Beside soft exudates, hemorrhages and venous beading are often present near ischemic areas (Ashton 1963). Large blot hemorrhages probably represent hemorrhagic infarcts; beading and formation of venous loops represent a preproliferative response to local ischemia.
The presence of soft exudates, large intraretinal hemorrhages, venous beading and intraretinal microangiopathy (dilated irregular retinal vessels) collectively is called preproliferative retinopathy. It is an ominous clinical sign that new vessels will develop within a year.
It is hypothesized that the stimulus for new vessel formation arises in the nonperfused areas (Kohner et al. 1976). Once the retina becomes hypoxic, it probably elaborates an angiogenic factor that induces new vessel formation. These new vessels tend to develop in close proximity to areas of nonperfusion. They originate usually, but not invariably, from veins. The extent of capillary nonperfusion is a major determining factor in the formation of new vessels on the optic disc and at the surface of the retina (Shimizu et al. 1981). Nonperfusion is more extensive in patients with disc neovascularization than in patients with retinal neovascularization.
Once neovascularization has developed and the proliferative phase has set in, rapid visual loss may occur by hemorrhages from the newly formed vessels. The late phase of proliferative retinopathy consists of vitreous hemorrhage, fibrous proliferation, traction retinal detachment and neovascular glaucoma. This condition can be avoided in most patients if photocoagulation treatment is given early.

1.1.2. *Cross-sectional studies*

Palmberg and co-workers (1981) determined the cross-sectional natural history of retinopathy in 461 insulin-dependent diabetics by means of stereophotography and angiography. Retinopathy was not present at diagnosis of diabetes. After a lag period the prevalence of retinopathy reached 50% at just over seven years duration and approached 90% at 17-50 years duration.

Proliferative retinopathy was first seen at 13 years duration and its prevalence rose to 26% at 26-50 years duration of the disease.
Prevalence of retinopathy increased with duration of diabetes in the 173 type I diabetic patients studied by Frank and co-workers (1982). Stereofundusphotography and fluorescein angiography was performed by a standardized protocol. A subject was considered to have retinopathy if either or both of the 2 methods were positive for retinopathy. One % of the patients had diabetic retinopathy 0-4 years after diagnosis of diabetes, 25% after 5-9 years and 67% 10-16 years after the onset of diabetes mellitus. There were no cases with retinopathy younger than 13 years old, or with less than 4 years duration of diabetes.
The Wisconsin epidemiologic study of diabetic retinopathy included 996 insulin-taking, diabetic persons with age at diagnosis less than 30 years (Klein et al. 1984C). Persons were examined using stereoscopic fundus photographs of seven standard fields of both eyes. The prevalence of retinopathy was 17% in patients with diabetes for less than 5 years and 97.5%, 15 or more years after diagnosis of diabetes. Proliferative retinopathy varied from 1.2% to 67% in persons with diabetes existing for less than 10 years and 35 or more years respectively.
Table 1.1 summarizes the results of the cross-sectional studies.

table 1.1. Retinopathy prevalence by duration of diabetes.

first author/ year of publication	method of examination	number of patients	duration of diabetes (yrs)	prevalence of retinopathy (%)
Palmberg et al. 1981	stereophotography and angiography	461	0-3 6-7 17-50	7 48 90
Frank et al. 1982	stereophotography and angiography	173	0-4 5-9 10-16	1 25 67
Klein et al. 1984C	stereophotography	996	0-5 15-30	17 97.5

1.1.3. *Longitudinal studies*

Few longitudinal studies have been reported in which a cohort of patients was followed prospectively (Gerritzen 1973; Pirart 1978; Diabetic retinopathy study 1976; Nielsen 1984; Klein et al. 1984A). Comparison of the studies is difficult because every author used his own classification of diabetic retinopathy. Other differences contribute to this difficulty, for instance the method of examination. In some studies only ophthalmoscopy was per formed to examine the fundus (Pirart 1978) while other studies use stereoscopic fundusphotography (Diabetic retinopathy study 1976; Klein et al. 1984A). One of the studies has been performed in selected patients (Diabetic retinopathy study 1976); sometimes the type of diabetes has not been described (Gerritzen 1973; Pirart 1978).

Gerritzen (1973) found 48% progression of retinopathy after an observation period of 8 years in 459 patients. In 38% retinopathy remained stable and in 14% it regressed.

A correlation between incidence and prevalence of retinopathy and duration of diabetes was found by Pirart (1978). In this prospective study 4400 patients were studied between 1947 and 1973. After 25 years of diabetes 50% of the patients had retinopathy. The prevalence depends on the survival and the accumulation of affected patients with the passage of time. Each year more patients previously unaffected join the group of patients with retinopathy. In the course of 25 years, the annual incidence for retinopathy increased from 3 to 13%.

Over a period of one year 24% progression was observed in the 215 patients in the study of Nielsen (1984). In 30% retinopathy remained unchanged and in 46% retinopathy showed regression.

In the study of Klein et al. (1984A) fundusphotographs were graded according to an abbreviation of the Modified Airlie House classification (see chapter 1.5.3.). The Airlie House classification represents a joint effort from ophthalmologists both in the United States and Great Britain to find a generally accepted classification for diabetic retinopathy. In the present study the same detailed protocol to document retinopathy status as proposed by Klein et al. was used. Their study is discussed more in detail.

Klein et al. (1984A) studied the course of diabetic retinopathy in 191 insulin-dependent diabetic patients over a 6-year period. The duration of diabetes was at least 5 years, the mean duration 14.9 years. Stereoscopic colour fundus photographs of 7 fields in each eye were graded using an 11-step grading scheme. At initial visit 18.3% of all patients had no retinopathy; 69.2% had a nonproliferative retinopathy and 12.5% had a proliferative diabetic

retinopathy. Of all patients seen at the 2-year visit, 41.2% showed progression of one level or more on the grading scale, 19.2% showed progression of two or more levels. At the 6-year examination comparable rates were 75.0% and 58.4%. Of the patients with a moderate to severe nonproliferative retinopathy at the initial visit 72% had progressed to proliferative retinopathy in at least one eye after 6 years. The risk of progression was slightly greater for patients with soft exudates and intraretinal microvascular abnormalities. Of all patients 10.4% showed regression of one or more levels at the 2-year visit. At the 6-year follow-up examination 3.7% of all patients showed regression of retinopathy of one or more levels. After 2 years 39% and after 6 years 86% of the patients without retinopathy had developed nonproliferative diabetic retinopathy, none of them progressed to the proliferative stage.

1.1.4. *The course of diabetic retinopathy during pregnancy*

Pregnancy has been suggested as a possible cause of increased severity of diabetic retinopathy. In earlier years the risk of loss of vision from progression of retinopathy during pregnancy was considered to be very high (Beetham 1950) and diabetic women with retinopathy were often advised against pregnancy or its continuation.
In a review of literature, Rodman and co-workers (1979) analyzed 201 cases with no or nonproliferative retinopathy at the onset of pregnancy. Retinopathy in 17 patients (8%) progressed during pregnancy. Four of these 17 patients developed a proliferative diabetic retinopathy. This ratio is probably not different from a comparable nonpregnant diabetic population. Of 127 cases with proliferative retinopathy reviewed by Rodman et al. 1979, 32 patients (25%) experienced progression during their pregnancy. Since the natural history of proliferative retinopathy tends to progression in the nonpregnant state as well, this study leaves undecided the question whether or not pregnancy poses an additional risk.
In a controlled study Moloney et al. (1982) determined the influence of pregnancy on diabetic retinopathy in 53 insulin-dependent pregnant diabetic women. Thirty-nine nonpregnant diabetic women of childbearing age served as controls. During the 15-month study period there was only little change in the pattern of retinopathy in the control group. In the pregnant group 8 out of 20 patients without retinopathy developed nonproliferative retinopathy and 1 out of 30 women with nonproliferative retinopathy developed a proliferative retinopathy. The condition of all 4 patients with a pro-

liferative retinopathy deteriorated. Changes in retinopathy were most intense during the 20th to 28th week of pregnancy. Soft exudates developed in 14 (28.6%) of the pregnant patients. Six months after delivery non-proliferative retinopathy had regressed to initial levels and newly formed vessels showed some regression.
Soubrane and co-workers (1985) noted a permanent unfavourable influence of pregnancy in patients with no or minimal retinopathy. In this study an analysis of fluorescein angiography showed a higher number of microaneurysms 15 months after delivery as compared with initial examination, before the 15th week of pregnancy. It remains unclear whether the authors took into account the fact that the duration between these 2 examinations was about 2 years because also in nonpregnant diabetics retinopathy tends to progress during a 2-year period (Klein et al. 1984A).
Since the advent of photocoagulation, by which the fatal results of proliferative retinopathy can be prevented to a high degree, several investigators conclude that proliferative retinopathy is neither an absolute contra-indication to pregnancy nor an absolute indication for termination of pregnancy (Cassar et al. 1978; Horvat et al. 1980; Johnston 1980; Gerke et al. 1982). Photocoagulation therapy appears to be as effective in preserving vision for nonpregnant as for pregnant women (Hercules et al. 1980).
Klein et al. (1984B) studied the relationship between the number of pregnancies a woman had and the severity of diabetic retinopathy in a population-based sample of type I diabetic patients. The number of pregnancies was positively associated with the severity of retinopathy. However, after controlling for duration of diabetes, this relationship was no longer apparent.

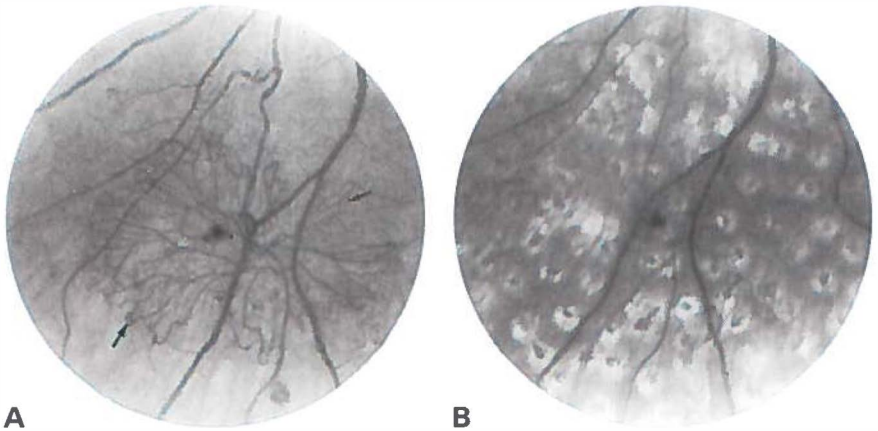
1.2. **Treatment of proliferative diabetic retinopathy**

1.2.1. *Photocoagulation*

In 1959 Meyer-Schwickerath made the first attempt to inhibit new growth of vessels in proliferative retinopathy by cauterizing them with light from a xenon arc focused on the retina.
In later years photocoagulation became the treatment of choice for proliferative diabetic retinopathy. It has totally replaced hypophysectomy, with its adherent complications and complex postoperative hormonal substitution therapy.

In the early 1960s investigators tried to obliterate neovascular tissue itself by focal photocoagulation (Wetzig et al. 1963). The first mention of lightcoagulation being used for its indirect effect on neovascularization - photocoagulation directed to nonperfused zones of the retina - was in 1964 by Meyer-Schwickerath.

Photocoagulation may be accomplished with either a xenon arc lamp or an argon laser. The xenon arc photocoagulator delivers a broad spectrum of white light and the argon laser delivers narrow spectral bands of blue and green light. The effects of photocoagulation depend upon the absorption of light energy by pigments. The eye contains 3 pigments: melanin, hemoglobin and xanthophyll. The light is mainly absorbed by melanin in the pigment epithelium and is subsequently converted to heat. As a result of this, destruction spreads both in the choriocapillaris and in the neuroretina. The effect of photocoagulation applied to hemoglobin in the retinal vessels depends upon the site of the blood within the retina. Coagulation of hemorrhages within the superficial retina will produce damage to the nerve fibre layer. The effect of coagulation of retinal vessels depends upon the blood flow in that vessel. Photocoagulation of arteries leads to spasm, applied to veins it results in occlusion. The yellow macular pigment absorbs the blue



figures 1.1 A-B.

A, newly formed vessels are visible in the midperiphery of the fundus. (arrows).

B, four weeks after photocoagulation treatment. The newly formed vessels show evident regression.

part of the argon laser light, resulting in macular destruction. This holds to a minor degree also for the short wavelengths of the xenon spectrum.
Photocoagulation therapy can be administered either in a panretinal or in a focal manner. Panretinal photocoagulation (extensive scatter treatment) is not aimed at the abnormal neovascularization itself, but at the surrounding ischemic retinal tissue. It appears that the extent of nonperfusion is closely and quite probably causatively associated with neovascularization from the retina and the optic disc (Shimizu et al. 1981).
In panretinal photocoagulation the retina is treated over a wide area, extending from the vascular arcades to the periphery and avoiding only a small area next to the optic disc and the macula. Total resolution of newly formed vessels usually occurs within 4 weeks (figs. 1.1A-B)(Doft et al. 1984).
It has been shown conclusively that prompt panretinal photocoagulation treatment is advisable in 2 groups of eyes:

1) eyes with new vessels and preretinal or vitreous hemorrhage.
2) eyes with new vessels on or within one disc diameter of the optic disc, equaling or exceeding 1/4 to 1/3 disc area in extent, even in the absence of preretinal or vitreous hemorrhage.

Using these criteria, panretinal photocoagulation reduces the risk of severe visual loss by 50% or more over a 2-year period (Diabetic retinopathy study 1978).
The mechanisms of inhibiting neovascularization by photocoagulation are incompletely understood. A major problem is that the stimulus for neovascularization is still unknown. In 1948 Michaelson first postulated the presence of a vasoproliferative or angiogenic factor in retinal tissue undergoing active neovascularization. It appeared probable that the angiogenic factor is produced by areas of ischemic retina (Ashton et al. 1954) though its identification had not yet been entirely successful (Patz et al. 1978; Ben Ezra 1979). Some of its molecular properties at least, a low molecular mass procollagenase activating material, have very recently been discovered (Taylor et al. 1986).
Panretinal photocoagulation would thus destroy the ischemic retinal areas, source of the angiogenic factor and at the same time restore oxygenation of the remaining retina. The relatively increased oxygen supply appears to occur by diffusion from the choroidal circulation (Weiter et al. 1980; Wolbarsht et al. 1980; Stefánsson et al. 1986).
Although the efficacy of photocoagulation for proliferative retinopathy has been demonstrated unequivocally (Diabetic retinopathy study 1976; 1978 and the British trial 1977), it is not without complications. Panretinal photo-

coagulation impairs peripheral and night vision because of widespread destruction of the peripheral retina. Impairment of peripheral vision was most prominent in xenon arc treated eyes. It can also impair central vision. According to the Diabetic retinopathy study (1978) visual acuity fell 1-4 lines in 10% of the treated eyes. In most cases this is because of macular edema (McDonald et al. 1985).
Whether photocoagulation treatment is effective in lowering the risk of blindness in patients with mild proliferative or preproliferative retinopathy is being studied in the Early Treatment Diabetic Retinopathy Study (ETDRS 1980). The results of this study have not yet been published.

1.2.2. *Vitrectomy*

In 1968, Kasner introduced the "open-sky" technique for removal of vitreous gel. After a large limbal incision the lens was extracted to provide access to the vitreous. The vitreous gel was engaged by cellulose sponge and excised with scissors. The intraocular volume was restored with a physiologic saline solution (Kasner et al. 1968). Kasner proved that the eye tolerates removal of large portions of the vitreous quite well.
In the past decade techniques for closed vitreous surgery through a pars plana approach have largely replaced the open-sky method. The first closed or pars plana vitrectomy was performed by Machemer. A sclerotomy is prepared 4 mm posterior to the limbus. No corneal incision is necessary and the lens is left in place (Machemer et al. 1971). To remove the vitreous gel, Machemer and co-workers designed a small instrument that incorporates infusion, suction and cutting mechanisms (Machemer et al. 1972). They later introduced endoillumination, a sleeve of fiberoptics around the instrument tip, which increases visibility of intraocular structures (Parel et al. 1974). In the past few years, instrumentation has been vastly improved and surgical techniques have been refined. Instruments of lighter weight and smaller size became available. The 4 systems of cutting, infusion, suction and illumination were divided among 2 or more separate probes (O'Malley 1975) (fig. 1.2.). This allowed miniaturization and standardization of the size of various instruments.
The major indications for pars plana vitrectomy in correcting the advanced complications of proliferative diabetic retinopathy are long-standing vitreous hemorrhage and traction retinal detachment. Since vitreous hemorrhage is often reabsorbed spontaneously and in view of the many operative and postoperative complications most surgeons wait 6 months or longer be-

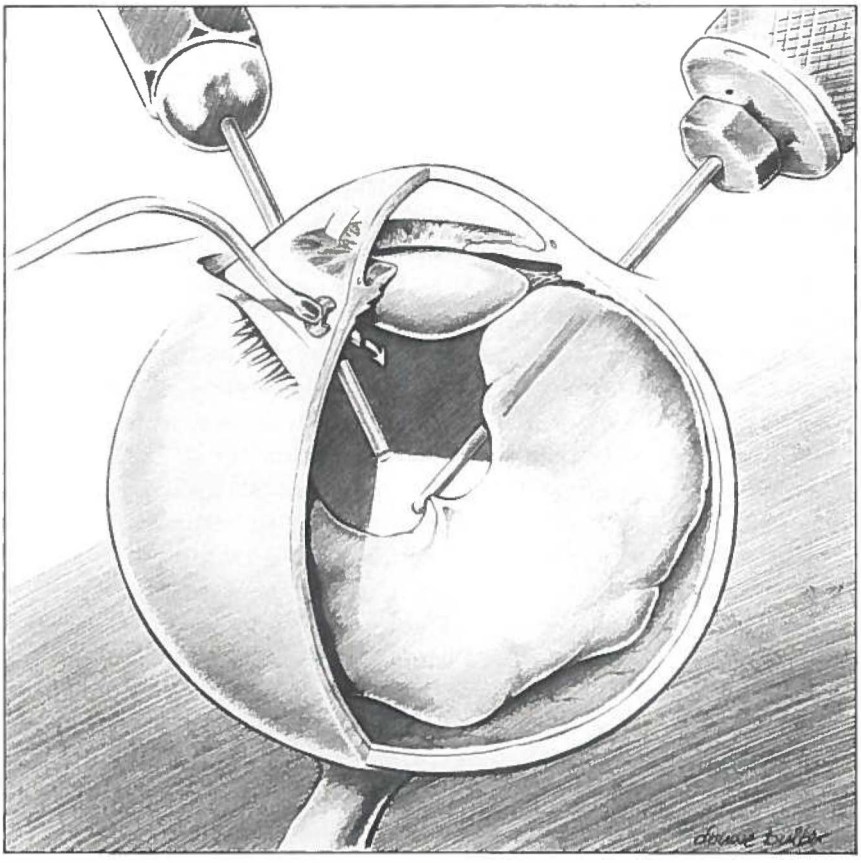


figure 1.2. The separate probes of infusion, suction-cutting and illumination systems are introduced through pars plana incisions.

fore performing vitrectomy. During the waiting period ultrasonography and electroretinography should be done frequently, to make sure that traction retinal detachment is not developing behind the hemorrhage. The decision to perform vitrectomy depends on the patient's age, the status of the fellow eye and an estimate of the potential visual function of the eye.
In the case of traction retinal detachment, vitreous surgery is not recommended in eyes with extramacular traction detachment. Unless the macula becomes involved, observation is for these patients the best choice. If the macula becomes detached, vitreous surgery is considered (Charles et al. 1981).

The benefits of vitrectomy in nonabsorbing vitreous hemorrhage or traction retinal detachment, secondary to proliferative diabetic retinopathy, have been reported extensively (Mandelcorn et al. 1976; Peyman et al. 1978; Michels 1978; Blankenship et al. 1979). The visual outcome depends much on the specific indication for surgery and the complexity of the vitreoretinal abnormalities. Eyes with only vitreous hemorrhage have the best prognosis. Improved vision has been achieved in 66% to 82% of these cases. When both vitreous hemorrhage and traction retinal detachment are present the prognosis is severely diminished. Visual improvement could be achieved only in 25% of these cases (Machemer et al. 1981).

Follow-up studies have shown that many patients who had a successful result at 6 months postoperatively tended to remain stable for a long period (Aaberg 1981). A 10-year follow-up study of 72 vitrectomies for diabetic retinopathy has recently been reported (Blankenship et al. 1985). Of the 202 pars plana vitrectomies performed 72 were available for 10-year follow-up examinations. Of these 42% maintained 6/60 or better visual acuity through the 10 years. The vitreous cavities remained clear in 67% of the eyes and fundus neovascularization did not recur.

Complications associated with vitreous surgery are more frequent and often more serious than those associated with other ophthalmic surgical procedures. The most common complications are creation of retinal holes and severe intraocular bleeding. Posterior retinal tears occur in 10%-15% of eyes with complex vitreoretinal anatomy (Michels 1978). Postoperatively the development of rubeosis of the iris, a precursor of neovascular glaucoma, is most feared. It is the severest type of glaucoma and usually occurs 2-12 weeks after vitrectomy. The incidence of neovascular glaucoma is twice as high in aphakic eyes as in phakic eyes (Blankenship et al. 1979; Aaberg 1981). Blindness caused by neovascular glaucoma occurs in about 10% of the cases after vitreous surgery (Mandelcorn et al. 1976; Michels 1978; Peyman et al. 1978).

A multicenter, randomized clinical trial was designed (The Diabetic Retinopathy Vitrectomy Study: DRVS) to determine the proper timing for vitrectomy following vitreous hemorrhage in diabetics. Eligible eyes are randomly assigned to early vitrectomy (1 to 6 months after occurrence of a severe vitreous hemorrhage) or deferral of vitrectomy for one year. Two-year results of the study have recently been reported (Diabetic retinopathy vitrectomy study 1985). Involved were 616 eyes of type I and type II diabetics with recent severe vitreous hemorrhage, reducing visual acuity to 5/200 or less for at least one month. In patients with type I diabetes, there was a clear-cut advantage for early vitrectomy. After 2 years of follow-up, 36% of

the patients in the early treatment group had a visual acuity of 10/20 or better, versus 12% in the deferral group. No such advantage was found in the type II diabetics (16% in the early group versus 18% in the deferral group).

1.3. **Effect of metabolic control on diabetic retinopathy**

The relationship between the control of hyperglycemia and the evolution of diabetic retinopathy is controversial. This is understandable in view of the lack of objective criteria to define glycemic control, the unpredictable course of the fundus changes and the lack of a uniform classification.
Benefits of strict blood sugar control in preventing, delaying or decreasing the severity of retinopathy have been reported extensively. In a 25-year study on 4400 diabetics, Pirart (1978) found less retinopathy in well-controlled patients than in those with poor control. Constam (1977) studied 1107 diabetics and observed a slowdown of progression of retinopathy in the well-controlled patients. A positive correlation between the development of retinopathy and the degree and duration of glycemic exposure was found by Dornan et al. (1982). In a study concerning 181 young adults with type I diabetes, 25 with poor control had retinopathy and an increased capillary basement membrane thickness, measured in muscle biopsies. After a well-controlled period of one year capillary basement membrane thickness diminished and retinopathy stabilized (Jackson et al. 1982). A statistically significant relationship between blood sugar control and the severity of diabetic retinopathy was found only in patients with diabetes diagnosed before 30 years of age by Schanzlin et al. (1979). The effect of multiple daily insulin injections on the course of diabetic retinopathy was studied in 42 type I diabetic patients by Job et al. (1976). The patients were randomly assigned to single or multiple daily insulin injections. Patients receiving multiple insulin injections showed better diabetic control compared with those receiving single injections. During a mean follow-up period of 3 years, the mean yearly progression in the number of microaneurysms was significantly less in the multiple injection group. However, the study was reanalysed and the results were modified (Ashikaga et al. 1978). After modification no difference in progression of retinopathy was found between the 2 treatment groups. In an animal model alloxan-diabetic dogs with good blood sugar regulation show significant reduction in incidence and severity of microvascular lesions (Engerman et al. 1977).
No statistical relationship however, between progression of retinopathy and mean blood sugar levels was reported by other investigators (Knowles

et al. 1965; Adnitt et al. 1970). A relation between metabolic control and diabetic retinopathy only early in the course of diabetic retinopathy was observed by Burditt et al. (1968).
It appears that a relationship between the degree of blood sugar control and the development of microangiopathy has not yet been conclusively proved. All ophthalmologists have met poorly controlled diabetic patients with minimal retinopathy and patients with well-controlled diabetes who became blind. Since even the most strict control of blood sugar does not approach the physiologic situation, all studies which compare good with poor control are studies of diabetics under abnormal, nonphysiologic metabolic regulation. The question will not be resolved until methods of glucose regulation approaching the physiologic state are available. Finer adjustment of the insulin dosage has been emphasized in recent years by means of multiple daily insulin injections and self-control. The latest development and the most physiological method of glucose regulation now available in ambulatory diabetic patients is continuous subcutaneous insulin infusion (CSII).

1.4. **Continuous subcutaneous insulin infusion (CSII)**

1.4.1. *Principles of CSII*

In 1977 Pickup and co-workers introduced continuous subcutaneous insulin infusion (CSII) in insulin-requiring diabetic patients. They demonstrated that long-term (near)-normoglycemia can be achieved in ambulatory conditions by means of CSII (Pickup et al. 1977, 1978 and 1979B).
CSII is an open-loop infusion system without glycemia-regulated feedback. This form of treatment resembles that of the traditional subcutaneous injections. The patient closes the open-loop by selfmonitoring blood glucose.
Insulin is administered according to a predetermined schedule based on regularly calculated blood glucose values. The daily dose of insulin is divided into a basal infusion rate and bolus injections. The bolus injections are administered 15 to 30 minutes before the start of a meal. The Mill Hill infusor used by Pickup and co-workers is a portable, battery-driven, miniature syringe pump. The pump is fitted with a 1-3 ml disposable plastic syringe. In the present study the Mill Hill infusor and the Auto syringe AS 6C was used (fig. 1.3.). The device can be conveniently worn on the

figure 1.3. Auto syringe AS 6C.

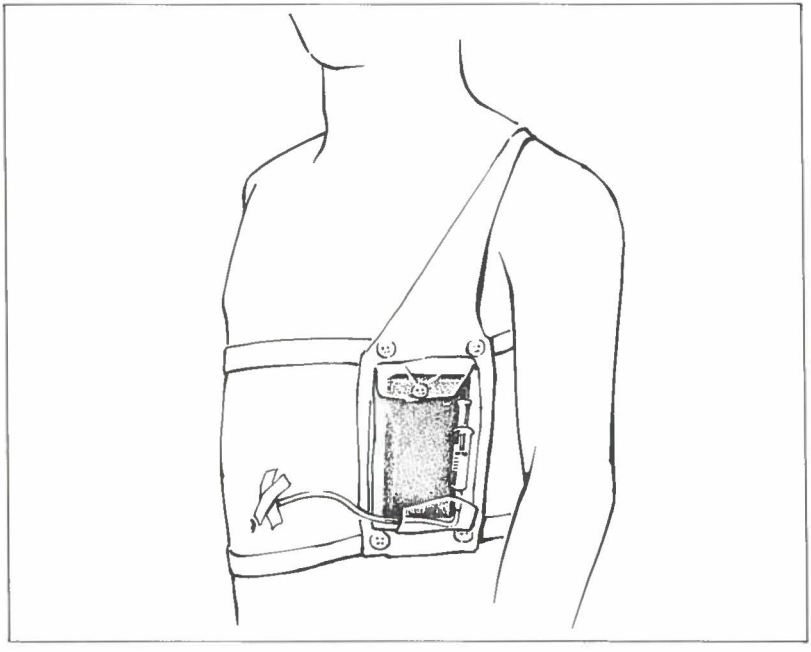


figure 1.4. Insulin infusion pump worn on the body in a holster.

body in a holster (fig. 1.4.). Insulin is delivered through a thin polythene catheter implanted in the subcutaneous tissue of the anterior abdominal wall by a butterfly needle.
Continuous subcutaneous insulin infusion pumps are now widely available for achieving intensive glycemic control of diabetes (Mecklenburg et al. 1982). In 1982, 3500 diabetic patients were using insulin infusion pumps in the United States (Teutsch et al. 1984). The number of patients treated with CSII in the Netherlands is about 500.

1.4.2. *Indications of CSII*

At present there are no absolute indications for treatment with CSII. There are however situations where the treatment had been shown to be beneficial.
The American Diabetes Association (ADA) formulated the indication for CSII treatment as follows:
"Continuous subcutaneous insulin delivery with a portable insulin infusion pump has been shown to be effective as a long-term outpatient procedure in the following situation: failure to achieve an acceptable level of diabetic control in certain type I diabetic subjects with unusual fluctuations in blood glucose levels, despite intensive efforts with proper diet and multiple injections of insulin in single or mixture form and high patient motivation and compliance" (American Diabetes Association 1982).
Contra-indications are not fully documented and agreed upon. Patients with poor social, emotional and psychiatric backgrounds should not be offered this treatment. The motivation of diabetics for treatment with CSII is quoted as being more important to a favourable response than their education or intelligence (Pickup et al. 1981).

1.4.3. *Effect of CSII on metabolic control*

Blood glucose concentrations are rapidly brought into the near-normal range by CSII (Pickup et al. 1978, Pickup et al. 1979B, Tamborlane et al. 1979A, Champion et al. 1980). After just a few days of CSII treatment most patients have stable blood glucose levels. Home blood glucose monitoring and HbA_1 measurements confirm that (near)-normoglycemia can be maintained throughout CSII treatment. Correction of glycemia by means of

CSII is accompanied by improved daily profiles of several intermediary metabolites such as lactate, pyruvate, 3-hydroxybutyrate and of serum cholesterol, triglycerides and free fatty acids (Pickup et al. 1979A). Plasma glucagon levels are reduced towards the normal range (Raskin et al. 1979) and both the exaggerated level of plasma growth hormone and catecholamine responses to exercise are reduced by CSII treatment (Tamborlane et al. 1979B). Furthermore somatomedin levels increase and growth hormone concentrations decrease during CSII treatment (Tamborlane et al. 1981).

1.4.4. *Effect of CSII on diabetic retinopathy*

1.4.4.1. Case reports

Three early case reports illustrate that the course of diabetic retinopathy can improve after normalization of blood glucose levels.
A 24-year-old type I diabetic woman showed improvement of severe proliferative retinopathy after 3 months of treatment with a portable infusion pump and an intravenous catheter (Irsigler et al. 1979). Fluorescein angiography revealed reperfusion of previously nonperfused areas and regression of vaso-proliferations. This is remarkable in view of the fact that 6 months after the start of treatment the patient developed neovascular glaucoma, leading to blindness (Kritz et al. 1981).
Reversal of retinopathy, as the result of normoglycemia by means of CSII, was reported by White et al. (1981). A 20-year-old woman with poorly controlled diabetes achieved good blood sugar levels with CSII. After 5 weeks of constant normoglycemia fluorescein angiography showed revascularization in some areas of previous non-perfusion and a reduction in capillary dilatation.
Regression of nonproliferative retinopathy in a type I diabetic patient, 8 weeks after the start of CSII was observed by Little (1981).

1.4.4.2. Non-randomized clinical studies

The efficacy of good blood sugar regulation by means of CSII, as related to improvement of diabetic retinopathy has not been conclusively proved in larger studies. On the contrary, most studies found progression of retinopathy during a treatment period of 6 to 18 months.
Thirty eyes of 15 type I diabetic patients were observed during 11-23 months of CSII treatment (Puklin et al. 1982). None of the patients showed regres-

sion of microvascular abnormalities. Ten eyes without diabetic retinopathy at entry visit remained free of lesions. One out of 8 eyes with nonproliferative diabetic retinopathy progressed to proliferative retinopathy. Eleven out of 30 eyes had a proliferative retinopathy at the start of the study. One of these eyes progressed to blindness and in five a vitreous hemorrhage occurred.

Lawson et al. (1982) treated 12 diabetic patients with CSII during 4-19 months. All patients had either proliferative or preproliferative diabetic retinopathy. Out of the 24 eyes 20 deteriorated with initiation of neovascularization in 12 eyes and progressive growth of new vessels in 8 eyes.

Regression of proliferative retinopathy was reported in 2 out of 10 eyes after 9 months of CSII (Segato et al. 1982). Eight of the 10 eyes had received panretinal photocoagulation treatment prior to CSII. No significant alterations were found in these eyes. The two untreated eyes however showed improvement of proliferative lesions during CSII treatment.

All 9 patients reached normal HbA_1 levels during CSII treatment over a mean period of 17 months in the study of Waldhäusl et al. (1983). Prior to CSII, 6 patients had no retinopathy, 2 had a nonproliferative and 1 had a proliferative retinopathy. During CSII treatment, 2 patients developed a proliferative diabetic retinopathy, in 1 of them leading to blindness. The patient with a proliferative retinopathy remained stable.

Prior to CSII treatment 8 insulin-dependent diabetic patients were observed during a control period of 6 months by Kelly et al. (1984). The control period was characterized by conventional insulin injections and each patient served as his or her own control. After that period patients were treated for 6 months with CSII. In neither treatment period an eye progressed from nonproliferative diabetic retinopathy to proliferative diabetic retinopathy. There was no significant beneficial or harmful effect during CSII treatment compared to conventional insulin therapy.

Bernsmeier et al. (1984) followed 37 type I diabetic patients treated with CSII during 1 year or longer. Three patients with a nonproliferative diabetic retinopathy and a duration of diabetes less than 10 years improved during CSII treatment. In the group of patients with duration of diabetes of more than 10 years, 3 patients developed a nonproliferative retinopathy.

Table 1.2. summarizes the results of the various nonrandomized clinical trials. Since most investigators use a different classification of retinopathy the results were converted to a simple classification so that comparisons can be made. In all studies mean HbA_1% fell to normal or near-normal levels with exception of the study of Kelly. In this study metabolic control improved but did not normalize under CSII.

table 1.2. Results, reported by various authors, of non-randomized clinical trials, concerning the effect of CSII on the course of diabetic retinopathy.

first author/ year of publication	mean CSII treatment period (months)	mean duration of diabetes (yrs)	ophthalmological examination	number of eyes	stage of retinopathy					
					no DR	mild NPDR	PPDR	PDR	progression of PDR with or without VH	blindness
Puklin et al. 1982	18	15.8	photography angiography	30	10	8	1	11	→ 5	
										→ 1
						→		1		
Lawson et al. 1982	11	16.6	photography angiography	24			15	9	→ 8	
							→	12		
Segato et al. 1982	9	—	angiography	10				10		
							2 ←			
Waldhäusl et al. 1983	17	12.4	photography	18	12	4		2		
						→		2		
						→				2
Kelly et al. 1984	6	11.8	photography	16	5	8	2	1		
					→	2				
						1 ←				
Bernsmeier et al. 1984	12	—	photography angiography	74	28	42		4		
					→	6				
					6 ←					

arrows: pointing right indicate deterioration; pointing left indicate improvement.
DR: diabetic retinopathy; NPDR: nonproliferative diabetic retinopathy;
PPDR: preproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; VH: vitreous hemorrhage.

1.4.4.3. Prospective randomized trials

Four randomized, controlled trials have been performed to examine the effect of CSII-induced strict control versus conventional insulin treatment. The duration of the studies varied from 8-12 months.
The first report was presented by the Steno Study Group (1982). The effect of 6 months of strict metabolic control was studied on eye and kidney function. Thirty-two insulin-dependent diabetics with advanced nonproliferative retinopathy were randomized either to CSII or conventional treatment. Retinal function was measured by means of macular recovery time (nyctometry), oscillatory potential (electroretinography) and fluorophotometry. The HbA_1% fell in both groups of patients but the fall was greater in the CSII group. A significant difference of HbA_1% was apparent after 2 months. The HbA_1% in the CSII group fell from 9.6 to 6.7% versus 8.8 to 8.0% in the conventionally treated group. Retinal function improved in the CSII group after 4-6 months of CSII treatment and deteriorated in the conventional treatment group. However, no information is given about the fundus appearance during the first 6 months of CSII treatment.
Thirty of the 32 patients were followed during another 6 months. After 1 year of CSII treatment a deterioration of retinopathy, as assessed by fundusphotography and fluorescein angiography was observed in 10 patients in the CSII group and in 5 patients in the conventional treatment group (Lauritzen et al. 1983). The strongest deterioration was observed in patients with the best glycemic control. The most common finding in deterioration was the appearance of soft exudates, hemorrhages, microaneurysms and capillary-free areas. However, despite deterioration of retinal morphology, retinal function improved with CSII treatment and deteriorated in the group with conventional treatment.
In another prospective randomized trial 65 insulin-dependent diabetic patients, with mild nonproliferative diabetic retinopathy were studied in a prospective multicenter randomized trial (Kroc Collaborative Study Group 1984). The patients were randomly assigned to CSII or conventional injection treatment. Patients were observed during 8 months. In the CSII group HbA_1% fell dramatically during the first 2 months of treatment (from 10.3 to 8.2%) and remained at a mean level of 8.0%. HbA_1% remained unchanged during conventional treatment (mean 10.1%). The overall distribution of retinopathy levels did not differ significantly between the 2 treatment groups. During the observation period, the level of retinopathy progressed in both groups. Deterioration of retinopathy as assessed by fundusphotography was greater in the CSII group (15 out of 32 patients) than in the

conventional treatment group (9 out of 33 patients). Progression was most commonly accounted for by the appearance of soft exudates and intraretinal microvascular abnormalities or both. The investigators concluded that abrupt transition to nearly normal levels of glycemic control is ineffective in slowing the progression of established retinopathy and that, on the contrary, it may induce the appearance of new lesions.

In a third prospective randomized study, the effect of tight blood glucose control on diabetic retinopathy was observed in 45 insulin-dependent diabetics during one year (Dahl-Jørgensen et al. 1985). The patients were divided into 3 treatment groups: a control group (2 insulin injections daily), a multiple injections (MI) group (4-6 times a day) and a CSII group. All patients had no or only mild diabetic retinopathy. A statistically significant improvement of mean blood glucose values and of HbA_1 levels was observed on CSII and MI. On evaluation of fluorescein angiograms retinopathy progressed in the CSII group during the first 3 months of treatment, but in the following period a statistically significant regression of retinopathy was registered. Half of the patients, treated with CSII and MI showed soft exudates after 3-6 months of treatment. These changes regressed in all but 4 patients after 12 months. One CSII treated patient developed transient proliferative retinopathy in both eyes after 3 months. CSII treatment in this patient was continued and within the following 3 months all retinal changes had regressed without laser treatment. The conventionally treated group showed a continuous progression of retinopathy. The investigators concluded that a large fall in blood glucose during initiation of intensified insulin treatment may lead to transient worsening of diabetic retinopathy in type I diabetics.

In the fourth study, the effect of improved metabolic control in type I diabetic patients with no or minimal diabetic retinopathy was studied by Olsen et al. (1985). Twenty-four patients were randomly allocated to conventional insulin therapy or CSII. Metabolic control was significantly improved in the CSII group. Mean HbA_1% fell from 8.9 to 7.0 in the CSII group and remained unchanged in the conventionally treated group (mean HbA_1% : 9.1). After 1 year, a progression of diabetic retinopathy was observed in 3 out of 12 patients in the CSII group and in 4 out of 12 in the other group. None of the patients in the CSII group developed soft exudates or new vessels and no accelerated progression of diabetic retinopathy was found.

Although methods of assessment of retinopathy and patients characteristics were different in the 4 randomized, controlled trials, the conclusions are similar. Apparently more rapid progression of retinopathy during CSII treatment was seen in patients with established retinopathy within the first

3-12 months of treatment. An abrupt large fall in blood glucose level may lead, in established retinopathy only, to progression of retinopathy. Some comments on the studies have to be made.

In the Steno study the broad range of background retinopathy was not classified. No distinction was made for instance between patients with microaneurysms and hemorrhages only and patients with a preproliferative retinopathy. So it remained unclear how severe retinopathy was in the patients who showed progression of retinopathy.

A second difficulty in the Steno study was the considerable overlap in metabolic control between the CSII group and the conventionally treated group. Comparison between the two groups did not show significant differences in retinal function and retinopathy. To resolve this problem all patients were ranked according to their mean blood glucose during the year and then divided into three groups: a well-regulated, a intermediately regulated and a poorly regulated group. The presentation of the results of two randomized groups together with the results by ranking patients according to 1-year blood glucose levels, is very confusing.

One of the techniques used by the Steno study group to observe retinal function was vitreous fluorophotometry. In advanced retinopathy a technique such as fluorophotometry is superfluous and can be misleading. A moderate leak from one single abnormal vessel causes considerable fluorescein leakage into the vitreous and fluorophotometric readings, in this situation, give no impression of the overall retinal involvement.

The observation period of all studies was short. To get an impression of the effect of CSII on the course of diabetic retinopathy, longer randomized studies are necessary. Both the Steno study group and the Kroc study group extended their study and reported their results of a 2-year follow-up. In both studies different levels of glycemic control were maintained when mean HbA_1 levels are compared. In the Steno study mean HbA_1% during 3-12 months and 13-24 months remained unchanged in both treatment groups (CSII group: 6.7%; conventional treatment group 8.3%). In the Kroc study however, mean HbA_1% increased in the CSII group from 8.0% after 8 months to 9.0% after 24 months. In the conventional treatment group these percentages were 10.1% and 10.8% respectively (Kroc study group 1984 and 1985B). During the second year, in both studies, the worsening of retinopathy in the CSII group was no longer apparent (Lauritzen et al. 1985; Kroc study group 1985A+B). Retinopathy progressed to a similar degree in the CSII and the conventionally treated group. Because of the increase of the mean HbA_1% during the second year, the results of the Kroc study are of limited value. Large-scale, prospective, randomized studies are needed to confirm these results.

1.5. **Classification of diabetic retinopathy**

1.5.1. *Introduction*

A number of classifications of diabetic retinopathy has been proposed but none is universally accepted. Some classifications appear too simple to be adequate, others too complex to be useful. The simplest and most universally accepted classification of diabetic retinopathy is nonproliferative retinopathy versus proliferative retinopathy. In recent years preproliferative retinopathy has been added.

1.5.2. *The Airlie House Classification*

A 12-member committee formulated the Airlie House classification during the U.S.P.H.S. Symposium on the Treatment of Diabetic Retinopathy held at Airlie House in Warrington (Davis et al. 1968). It represents a joint effort from workers both in the United States and Great Britain to find a comprehensive, generally accepted classification and grading system for diabetic retinopathy.
Five standard photographic fields were defined to include most of the fundus within 30° of the centre of the macula. The evaluation for nonproliferative retinopathy includes degree of hemorrhage or microaneurysms or both, hard exudates, soft exudates, venous abnormalities, intraretinal microvascular abnormalities and macular edema. For proliferative retinopathy the evaluation includes degree of neovascularization on the disc, neovascularization elsewhere, fibrous proliferation, preretinal hemorrhage and vitreous hemorrhage. Lesions amenable to photographic assessment are graded by reference to a standard colour photograph: grade 0, lesion absent; grade 1, lesions less severe than standard photograph; grade 2, lesion more severe than standard photograph. Other lesions are graded by reference to standard written descriptions.

1.5.3. *Modification of the Airlie House Classification*

In the Diabetic Retinopathy Study (DRS) a modification of the Airlie House classification is used (Diabetic retinopathy study 1972). The classification was modified for most lesions by dividing the broad severity spectrum com-

prehended in grade 1 into two parts, using a second standard photograph or a written definition. A "questionable" category was added to the grading scale. The original three-step scale became for most lesions a five-step scale and two additional standard photographic fields were added. Several minor lesions were added and a new section was included regarding involvement of the macula by edema and other lesions.

An adaptation of the Modified Airlie House classification of diabetic retinopathy is used in the Early Treatment for Diabetic Retinopathy Study (ETDRS). The further modifications in this classification provide additional steps in the grading scale for some lesions, separate other lesions previously combined in single categories and allow assessment of several additional lesions. Complete definitions are given in the Manual of Operations of the Early Treatment Diabetic Retinopathy Study (1980).

In the present study the ETDRS adaptation of the Modified Airlie House classification is used. The grading protocol is described in chapter 2.3.1.

CHAPTER 2

PATIENTS AND METHODS

2.1. **Patients**

All insulin dependent (type 1) diabetic patients, who were treated with CSII at the Department of Clinical Endocrinology of the University of Groningen in the period between November 1980 and December 1985, were referred to the Outpatient Clinic of the Department of Ophthalmology and contributed to this study.
The indications in the present study for CSII treatment were:

a. poor blood sugar control despite intensive conventional insulin treatment.
b. pregnancy.
c. meticulous blood sugar control in women who intended to become pregnant.

All patients had type I diabetes before the age of 30. None of the patients had urinary tract infections, a history of renal disease or heart failure.
Patients, in which an evaluation of the retina by means of fundusphotography was impossible, were excluded.
More information about the patients who were studied is given for each chapter separately under the heading "patients".
The possible risks and benefits of insulin infusion pumps were discussed extensively with the patients and all of them gave a written informed consent.

2.2. **Methods**

2.2.1. *Glucose control*

To allow thorough instruction and rapid determination of the optimal insulin dose, all patients were admitted to the hospital for initiation of pump treatment. The mean hospital stay was 7 days. CSII was performed according to the method described by Pickup et al. (1979B), using either a Mill Hill Infuser, model 1001 AM or HM (Muirhead Medical Products Ltd, London, UK) or an Auto-Syringe AS 6C infusion pump (Travenol, USA). The subcutaneous butterfly needle was replaced twice a week. Actrapid MC 40E/ml insulin (Novo Industri) was used throughout as the infusion fluid, diluted if necessary with Diluting Medium (Novo Industri).
During the first year of CSII 24 h blood glucose profiles were made every 2-3

weeks. After that period they were made every 6-8 weeks. At home patients took fingerprick samples at 3, 7 (fasting), 11, 14, 17, 19 and 23 h. They stored the blood samples in small plastic cups for measurement in the laboratory (Auto-Analyzer II, Technicon).
Glycosylated hemoglobin (HbA_1) was measured every 2-8 weeks by a colorimetric method (normal range 6-8.5 per cent). In pregnant patients HbA_1 was measured every 2 weeks.
The patients performed home blood glucose monitoring 3-8 times daily with Haemo-Glukotest 20-800 reagent strips (Boehringer-Mannheim, FRG). (Near)-normoglycemia (3-8 mmol/l) was aimed at in all patients. Patients were seen at the Diabetes Outpatient Clinic every 2-8 weeks. A 24 h telephone service was provided for urgent problems (Ballegooie et al. 1984B).

2.2.2. *Ophthalmological examinations*

Prior to CSII treatment each patient underwent an ophthalmological examination which included determination of best corrected visual acuity, slitlamp biomicroscopy, ophthalmoscopy, fundusphotography and fluorescein angiography.
During the first year of CSII treatment all patients were investigated every 4 months. After the first year patients were examined twice a year. Patients with severe retinopathy were examined at more frequent intervals. Pregnant patients had an ophthalmological examination every trimester of pregnancy and 3-6 months postpartum. Pregnant patients with preproliferative or proliferative retinopathy were examined every 4 weeks.

2.2.2.1. Case history

The department of Clinical Endocrinology presented the non-ophthalmological data of all patients.

2.2.2.2. Visual acuity

Visual acuity was determined with the Snellen test, standardized at 6 m. If present, refractive errors were corrected and the best corrected visual acuity was measured.

2.2.2.3. General ophthalmological examination

On slitlamp biomicroscopy of the anterior segment of the eye special attention was given to the presence of rubeosis iridis and lens opacities. The ocular fundus was examined through dilated pupils by means of indirect and direct ophthalmoscopy. Usually adequate mydriasis was obtained in about 10-20 minutes by instillation of one drop of Mydriaticum (Chibret) and one drop of phenylephrine 2½%.

2.2.2.4. Fundus photography

Colour fundus photographs of both eyes were taken with a Zeiss funduscamera FK 30 or FK 50 loaded with Kodak Ektachrome professional 64 daylight film. Each set of photographs consisted of seven standard 30° photographic fields as used in the DRS study (Diabetic retinopathy study 1981B). The seven standard fields for the right eye are shown schematically in figure 2.1.

2.3. **Classification of diabetic retinopathy**

Grading severity of retinopathy from fundus transparancies in seven fields is the accepted standard method in clinical trials (Davis et al. 1985). Fluorescein angiograms, which were obtained according to the technique described by Oosterhuis and Lammens (1965) were not used for classification. They were needed to study the process of capillary closure and capillary leakage in suitable cases.

2.3.1. *Grading Protocol*

All photographs were double graded by separate observers. This grading consisted of a field-by-field, lesion-by-lesion evaluation of each slide, magnified in a 5× viewer and utilizing the ETDRS adaptation of the Modified Airlie House classification of diabetic retinopathy.
Results were recorded on the Detailed Colour Grading Form: ETDRS form 76 (ETDRS 1980: Manual of Operations). When the two graders dis-

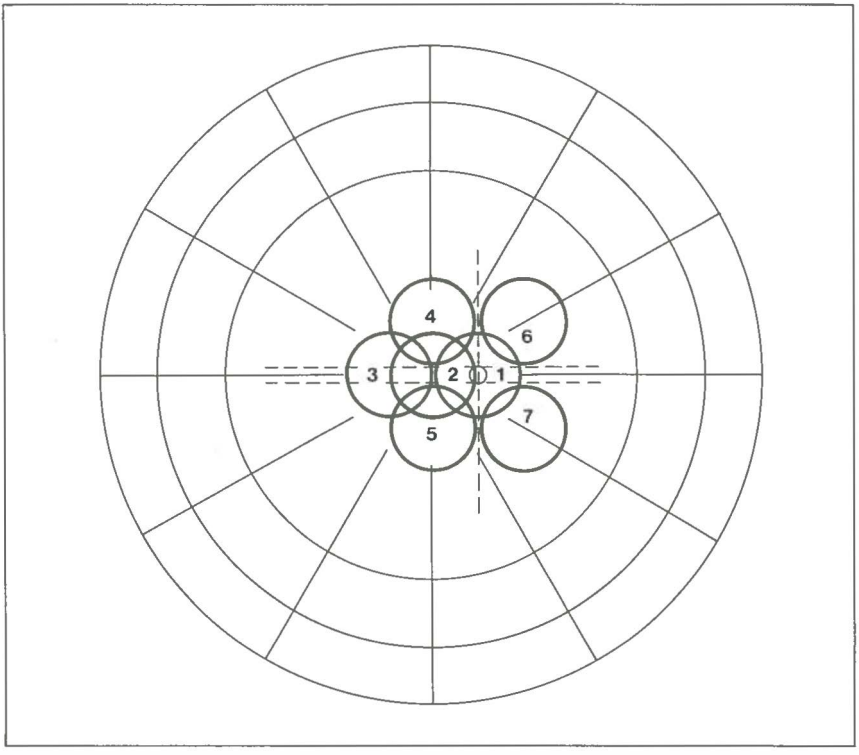


figure 2.1. Seven standard photographic fields for the right eye.

Field 1, Disc, with centre of disc at intersection of cross hairs; field 2, Macula, with centre of macula at intersection of cross hairs; field 3, Temporal to macula; field 4, Superior temporal; field 5, Inferior temporal; field 6, Superior nasal; field 7, Inferior nasal.

agreed, the fundus was regraded by both graders. If discrepancies remained, the case was referred to a third grader and differences were resolved by discussion. In this way nearly 5200 fundusphotographs had to be read. Photographs of both eyes of each patient from all visits were graded at the same sitting. This approach was chosen for its convenience and to allow recognition of unexpected changes in retinopathy status. This occurred sometimes when a lesion near the peripheral edge of a photographic field happened to be cut off in a series.

2.3.2. *Definitions of retinopathy levels*

For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions used in defining the retinopathy levels listed below. The definitions of the various lesions and the standard photographs are those of the Modified Airlie House classification.

level 1: no retinopathy

level 2: microaneurysms (one or more) only.

level 3: microaneurysms and one or more of the following: retinal hemorrhages, but total of hemorrhages and microaneurysms less than Standard Photo # 2A; hard exudates less than Standard Photo # 3; soft exudates questionably present; intraretinal microvascular abnormalities questionably present; venous beading questionably present or venous focal narrowing or loops definitely present.

level 4: microaneurysms and one or more of the following, but definition of level 5 not met: hemorrhages and microaneurysms $\geq$ Standard Photo # 2A; hard exudates $\geq$ Standard Photo # 3; soft exudates definitely present; intraretinal microvascular abnormalities definitely present; venous beading definitely present.

level 5: in fields 4 to 7 only, any three of the four following lesions: hemorrhages and microaneurysms $\geq$ Standard Photo # 2A in at least one field; soft exudates definitely present in at least 2 fields; intraretinal microvascular abnormalities definitely present in at least 2 fields; venous beading definitely present in at least 2 fields; **or** intraretinal microvascular abnormalities present in 4 fields and $\geq$ Standard Photo # 8A in at least 2 fields.

level 6: new vessels and/or fibrous proliferations (disc or elsewhere) or scars of photocoagulation (either "scatter" or confluent patches presumably directed at new vessels), or fundus obscured by vitreous hemorrhage.

The classification scheme used in this study is based on levels of retinopathy in both eyes. In this classification each patient is first classified according to the more severely involved eye and then allocated to one of two subgroups on the basis of the other eye: an equal level of retinopathy in the second eye (for instance 4/4) or a lower level in the second eye (for instance 4/<4). This results in an 11-step grading scheme as proposed by Klein et al. (1984A). The levels of retinopathy are as follows: 1/1, 2/<2, 2/2, 3/<3, 3/3, 4/<4, 4/4, 5/<5, 5/5, 6/<6, and 6/6. Classification of patients by retinopathy level in each eye, rather than simply by the worse eye, increases the number of

steps in the classification and therefore the sensitivity with which progression can be detected.
Progression of retinopathy was defined as an increase in the level of retinopathy to which the patient was assigned at initial visit. Because level 6/6 is the most severe level it is impossible within this classification scheme to demonstrate the course of proliferative retinopathy. Therefore the results of the patients with proliferative retinopathy had to be described separately.
The use of this grading scheme has an other limitation. A change in retinopathy level in the less severely involved eye cannot always be expressed. For example, a change in retinopathy level in the less severely involved eye of a patient classified in level 4/<4 from level 2 to level 3 is not considered as progression since the patient would still be classified in level 4/<4. To resolve this problem a 21-step grading scheme should be needed, which is too complex to be useful. Another way to express the retinal status is to calculate the mean retinopathy level in paired eyes. This method is not consistent with the usual clinical practice of characterizing patients by the more severely involved eye.

CHAPTER 3

THE EFFECT OF ONE YEAR IMPROVED GLYCEMIC CONTROL BY MEANS OF CSII ON THE COURSE OF DIABETIC RETINOPATHY

Partly published in:
Hooymans JMM, Ballegooie E van, Schweitzer NMJ, Doorenbos H, Reitsma WD, Sluiter WJ (1982). Worsening of diabetic retinopathy with strict control of blood sugar. Lancet ii:438.

Ballegooie E van, Hooymans JMM, Timmerman Z, Reitsma WD, Sluiter WJ, Schweitzer NMJ, Doorenbos H (1984). Rapid deterioration of diabetic retinopathy during treatment with continuous subcutaneous insulin infusion. Diabetes Care 7:236-242.

3.1. **Patients**

Diabetic retinopathy was studied in 35, type I diabetic patients during one year of CSII treatment. The group consisted of 14 men and 21 women. The

table 3.1. Patient data.

patient no.	age (yrs)/sex	duration of diabetes (yrs)	proteinuria ≥0.5 g/day
1	28/F	4	—
2	30/M	16	—
3	32/M	17	—
4	28/F	5	—
5	20/F	13	—
6	36/M	19	+
7	50/M	21	—
8	32/M	14	+
9	58/F	46	—
10	24/F	4	—
11	26/F	12	—
12	32/M	15	—
13	37/F	12	—
14	26/M	5	—
15	23/F	17	+
16	31/F	16	—
17	33/F	24	—
18	32/F	20	+
19	29/F	13	—
20	21/F	5	—
21	24/F	9	—
22	32/F	5	—
23	20/F	6	—
24	17/M	11	—
25	27/M	3	—
26	58/M	32	—
27	40/F	22	—
28	22/F	3	—
29	22/M	20	—
30	20/F	13	—
31	44/F	17	—
32	20/M	2	—
33	35/M	18	+
34	32/M	13	—
35	26/F	18	—

mean age at diagnosis of diabetes was 16.7 years (range 2-29). The average age, when started with CSII treatment was 30.4 years (range 17-58). The average duration of diabetes at the onset of CSII treatment was 14 years (range 2-46). Age, sex, duration of diabetes and presence of proteinuria at first examination are given in table 3.1.
Five patients had a diabetic nephropathy (proteinuria $\geq$ 0.5 g/day). Patient no. 18 used an antihypertensive drug, patient no. 13 and 21 used a contraceptive drug. The remaining patients used no medication other than insulin. Since pregnancy can influence the natural course of diabetic retinopathy (Moloney et al. 1982), pregnant patients were excluded, in order not to confuse the results of the study.

3.2. **Results**

3.2.1. *Results of glucose control*

The improvement in glucose control was reflected in a reduction of blood glucose and HbA_1 levels. The results of blood glucose control before and during CSII are given in table 3.2. The mean levels of each patient were used to calculate the mean values of the whole group. Individual results are to be found in table A-I (appendix).

table 3.2. Mean blood glucose values and mean HbA_1% (±SD) before and during CSII

mean blood glucose (mmol/l)		
	before CSII	11.8 ± 3.0
	during CSII	7.4 ± 1.8*
mean HbA_1%		
	before CSII	10.3 ± 2.4
	after 6 months CSII	7.7 ± 1.2*
	after 12 months CSII	7.6 ± 1.2*

* $P<0.01$ (Wilcoxon signed rank test for paired data. A P value < 0.05 was considered significant).

Severe hypoglycemia requiring intervention with intravenous glucose or intramuscular glucagon was reported in 5 patients (no. 1, 3, 6, 15 and 34). Patient no. 35 had an episode of diabetic keto-acidosis.

3.2.2. *Ophthalmological results*

Table 3.3. presents patients characteristics by retinopathy level in the worse eye before the start of CSII. The level of retinopathy increases with duration of diabetes.
Table 3.4. and figure 3.1. show the course of diabetic retinopathy during one year of CSII treatment.

table 3.3. Patient characteristics before CSII by level of retinopathy in the eye with the more severe retinopathy.

retinopathy level	no. of patients	mean duration of diabetes (yrs)	mean age at diagnosis (yrs)
1	8	5.1	20.0
2	7	12.0	18.8
3	5	14.8	18.2
4	7	17.1	11.7
5	1	19.0	17.0
6	7	21.7	14.4

figure 3.1. The course of diabetic retinopathy during one year of CSII treatment.

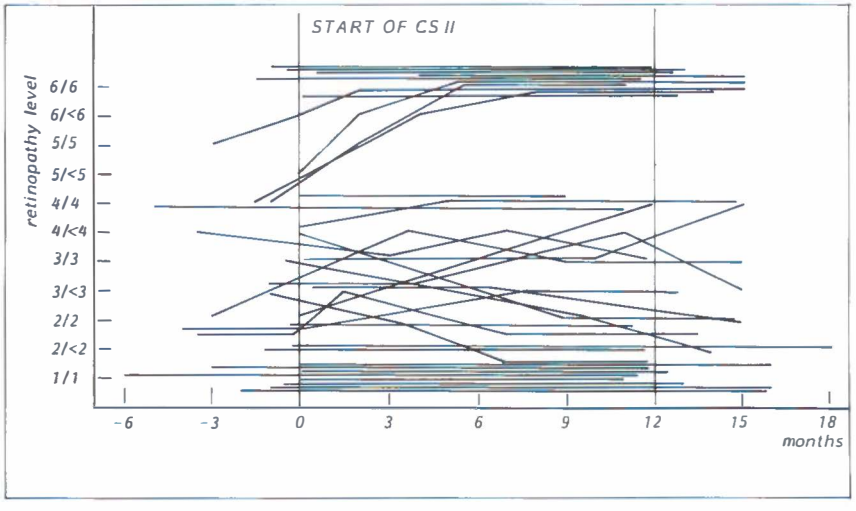


table 3.4. Level of retinopathy before and after 6 and 12 months of CSII treatment.

patient no.	level of retinopathy		
	before CSII	after 6 months CSII	after 12 months CSII
1	2/<2	2/<2	2/<2
2	4/<4	4/4	4/4
3	2/2	2/2	2/2
4	1/1	1/1	1/1
5	3/3	2/2*	2/<2
6	5/<5	6/6	6/6
7	2/2	—	4/4
8	4/4	6/<6	6/6
9	6/6	6/6	6/6
10	3/<3	1/1	1/1
11	1/1	1/1	1/1
12	6/6	6/6	6/6
13	3/3	3/3	4/4
14	1/1	1/1	1/1
15	4/4	6/6	6/6
16	6/6	6/6	6/6
17	6/6	6/6	6/6
18	6/6	6/6	6/6
19	4/<4	2/2**	2/2
20	2/<2	2/<2	2/<2
21	2/2	3/<3	3/<3
22	1/1	1/1	1/1
23	1/1	1/1	1/1
24	2/2	2/2	2/2
25	1/1	1/1	1/1
26	3/<3	3/<3	4/<4
27	4/4	4/4	4/4
28	1/1	1/1	1/1
29	4/<4	4/<4	3/3
30	3/<3	3/<3	2/2
31	2/2	4/<4	3/3
32	1/1	1/1	1/1
33	6/<6	6/6	6/6
34	6/6	6/6	6/6
35[x]	4/4	4/4	

* after 10 months.

** after 9 months.

[x] CSII treatment discontinued after 9 months.

3.2.2.1. Patients with nonproliferative retinopathy at the start of the study

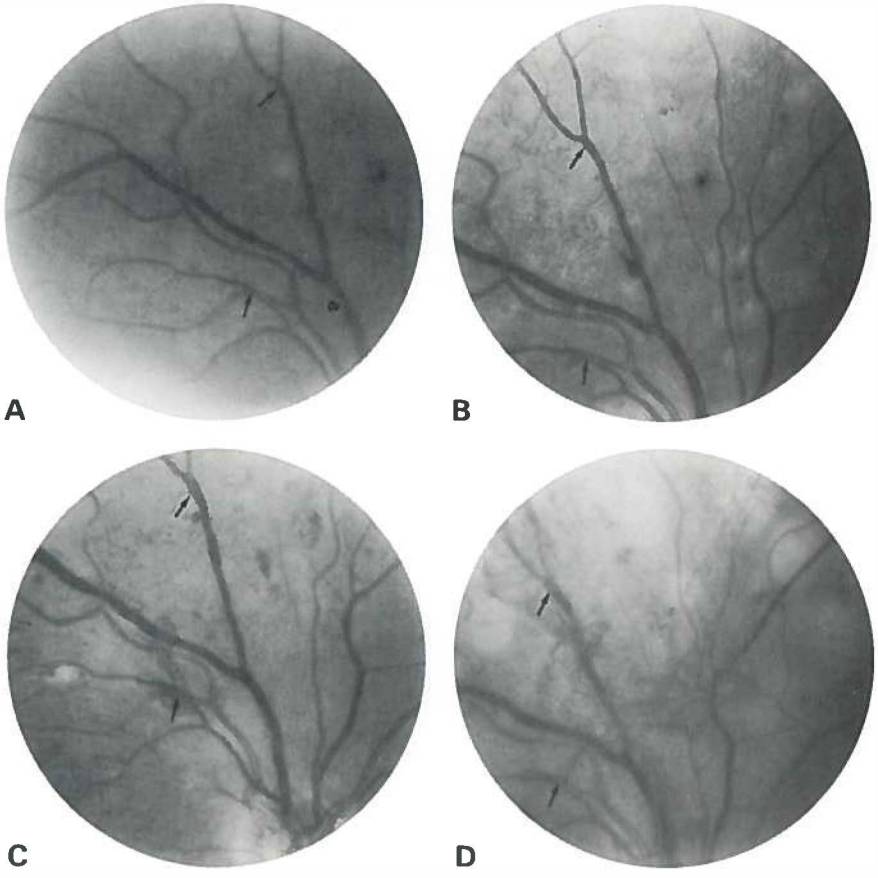
It is striking that within 2-6 months a severe proliferative retinopathy developed in 4 patients (no. 6, 8, 15 and 33) who at the entry into the study ranged from level 4/4 to 6/<6. Two of them developed new vessels on the optic disc and two others retinal new vessels (figs. 3.2 A-D and figs. 3.3 A-D). Panretinal photocoagulation was applied in all 4 patients. Despite photocoagulation treatment a vitreous hemorrhage occurred in 4 eyes of 3 patients (patient no. 6, 15 and 33) (figs. 3.4 A-B). Two eyes became blind due to a traction retinal detachment (patient no. 6 and 15).
Table 3.5. shows the clinical data and the HbA_1% prior to and during CSII treatment of the 4 patients who developed a proliferative diabetic retinop-

table 3.5. Clinical data of the patients who progressed to proliferative diabetic retinopathy during the first year of CSII treatment.

patient no.	duration of diabetes (yrs)	proteinuria ≥0.5 g/day	retinopathy level before CSII	HbA_1% before CSII	HbA_1% after 6 months CSII	HbA_1% after 12 months CSII
6	19	+	5/<5	11.8	8.2	8.3
8	14	+	4/4	12.2	7.2	7.9
15	17	+	4/4	10.2	9.6	7.7
33	18	+	6/<6	8.8	6.4	6.2

athy. Here we are struck by the similarity of these 4 patients. All had a long duration of diabetes (mean 17 years), a high level of retinopathy at the start of CSII treatment and a diabetic nephropathy.

In patients with a less severe retinopathy level (4/<4 or less) at the beginning of CSII, the appearance of soft exudates was the main sign of worsening of retinopathy during CSII treatment. This occurred in 6 out of 23 patients (no. 2, 7, 13, 26, 29 and 31). Soft exudates were found after 4, 5, 7, 11 and 15 months of intensified blood sugar regulation. Unfortunately patient no. 7 missed one visit, so it remains unknown at what time his soft exudates appeared.



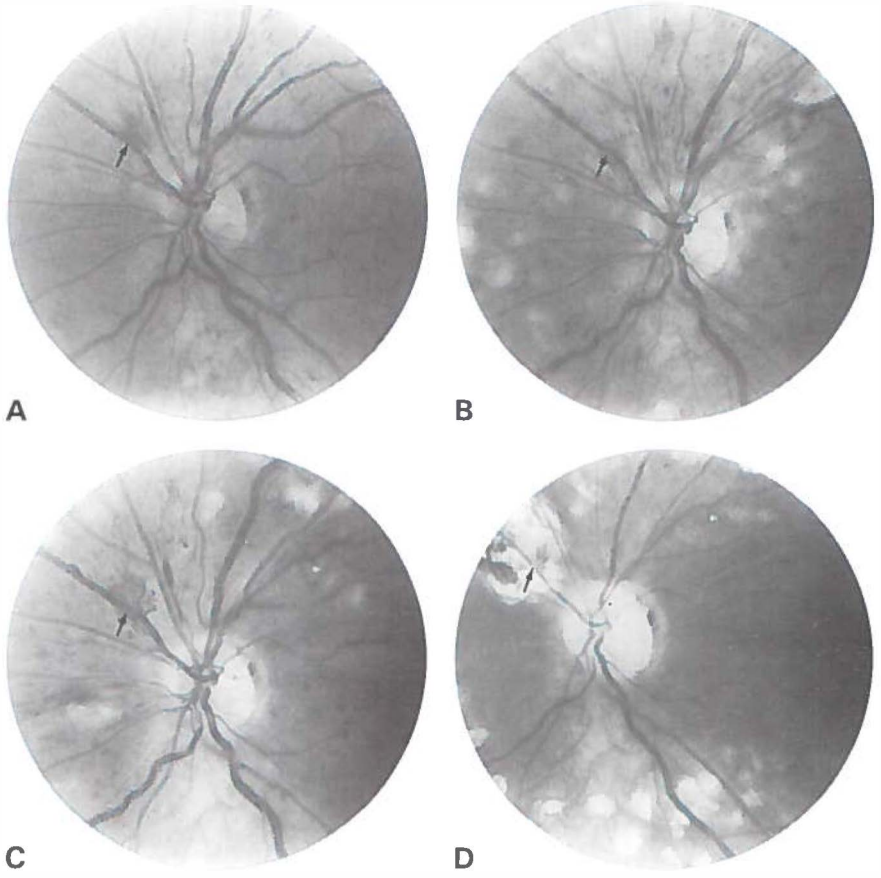
figures 3.2 A-D. Patient no. 15. Fundusphotographs of the right eye, superior temporal region. Arrows point to corresponding areas of the retina.

A, taken 2 weeks prior to CSII treatment. Soft exudates, intraretinal microvascular abnormalities and venous beading are present.

B, after 2 months of CSII treatment, showing evident progression of intraretinal microvascular abnormalities.

C, six months after the start of CSII. Retinal new vessels and newly formed vessels on the optic disc had developed.

D, marked progression and development of new vessels after 8 months of CSII treatment.



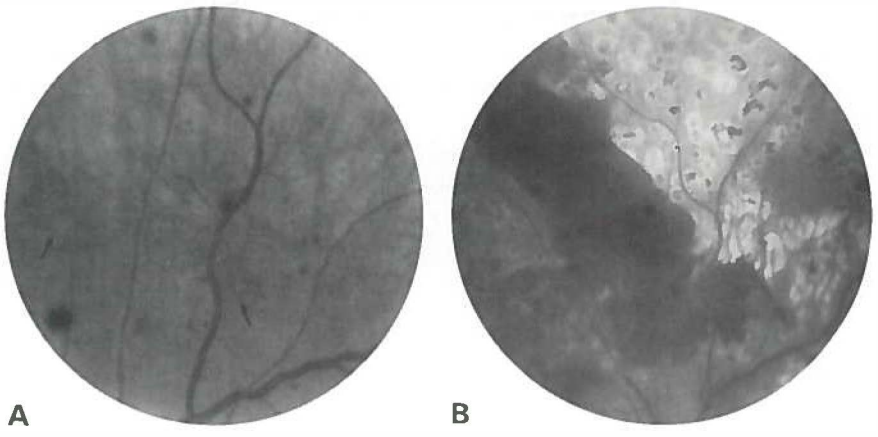
figures 3.3 A-D. Patient no. 8. Fundusphotographs of the left eye. Arrows indicate corresponding points.

A, taken 6 weeks before the start of CSII treatment. Flame-shaped hemorrhages and venous beading are present.

B, at 5 months on CSII treatment, retinal new vessels had developed nasal to the optic disc.

C, progressive growth of the newly formed vessels was observed 9 months after the start of CSII. Note venous beading and soft exudates.

D, taken 12 months after completion of photocoagulation treatment and 24 months after the start of CSII treatment. Retinopathy had regressed after photocoagulation.



figures 3.4 A-B. Patient no. 33. Fundusphotographs superior to the optic disc of the left eye.

A, taken at the start of CSII treatment. Two fronds of newly formed vessels (arrows) are visible.

B, a vitreous hemorrhage occurred after 12 months of CSII treatment, despite panretinal photocoagulation treatment.

Table 3.6. presents the clinical data and the HbA_1% before and during CSII treatment of the patients who developed soft exudates. All 6 patients had a long duration of diabetes (mean 20 years).

table 3.6. Clinical data of the patients who developed soft exudates during the first year of CSII treatment.

patient no.	duration of diabetes (yrs)	proteinuria ≥0.5 g/day	retinopathy level before CSII	HbA_1% before CSII	HbA_1% after 6 months CSII	HbA_1% after 12 months CSII
2	16	—	4/<4	13.0	6.1	8.7
7	21	—	2/2	12.1	8.3	9.6
13	12	—	3/3	9.7	8.8	7.8
26	32	—	3/<3	8.1	7.5	5.7
29	20	—	4/<4	8.7	7.2	6.8
31	17	—	2/2	10.1	7.6	6.3

It has to be mentioned that the fall of HbA_1% was of the same order for the patients who progressed to proliferative retinopathy, for those who developed soft exudates and those who showed no or only a minimal change in retinopathy level.
Apart from the 4 patients mentioned, who developed a proliferative retinopathy and the 6 patients who developed soft exudates, another 2 patients showed some deterioration. In these 2 patients (no. 3 and 21) a few small intraretinal hemorrhages were observed after 2 and 8 months of CSII treatment.

Special cases

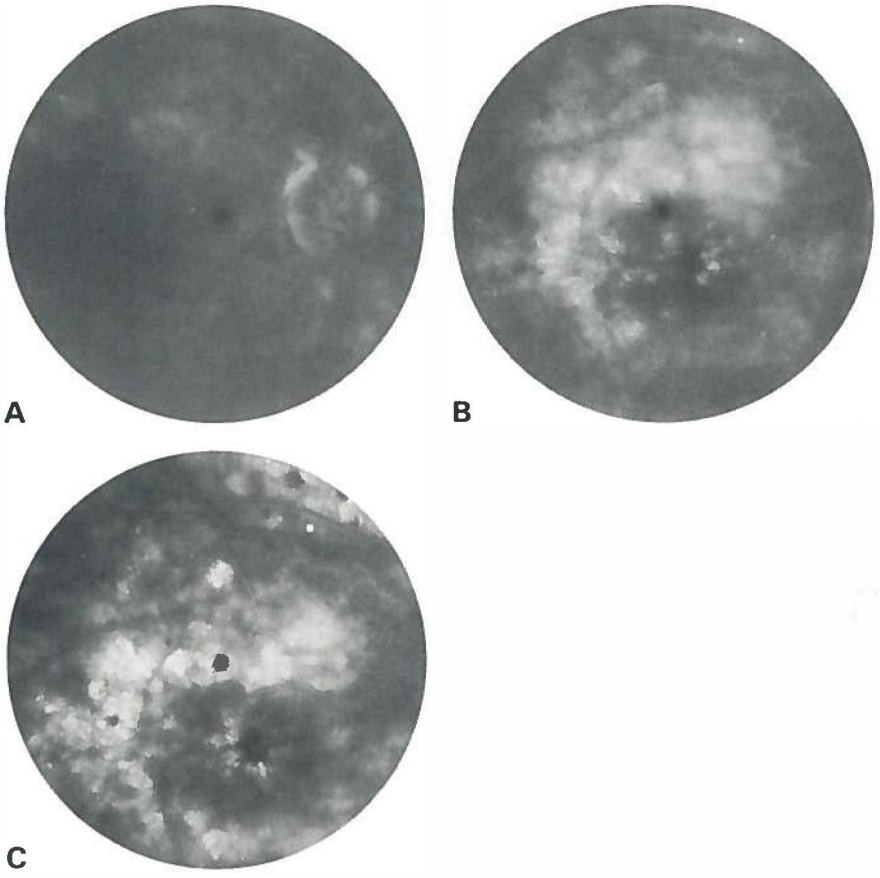
Two histories are mentioned because of the special course of retinopathy which could not be expressed in change of levels.

A diffuse capillary leakage in the macular area was observed on the angiogram of patient no. 35, 2 months prior to CSII treatment. After 6 months of CSII treatment a severe cystoid macular edema had developed in both eyes. Two months later the angiogram showed severe progression of macular edema (figs. 3.5 A-C). The level of retinopathy (4/4) remained unchanged.

At the start of CSII the left optic disc of patient no. 34 showed dilated capillaries and some hyperemia. Both eyes had received prophylactic photocoagulation prior to CSII, for extensive areas of capillary occlusions. The patient therefore had to be classified as 6/6 (see definitions of retinopathy levels: chapter 2.3.2.). If we leave out of consideration the scars of photocoagulation, the level of retinopathy should be 5/5. Within the first 4 weeks of CSII, a marked swelling of the left optic disc with nerve fiber hemorrhages and cystoid macular edema had developed. The visual field showed a nerve fiber bundle scotoma and the visual acuity dropped from 1.2 to 0.1. The optic disc became atrophic within 6 weeks of CSII treatment (figs. 3.6 A-C). Retinopathy level however remained unchanged in both eyes during the observation period.

3.2.2.2. Patients with proliferative retinopathy at the start of the study

At the start of the study 5 patients (no. 9, 12, 16, 17 and 18) had a proliferative retinopathy in both eyes. Patient no. 34 had a preproliferative retinop-

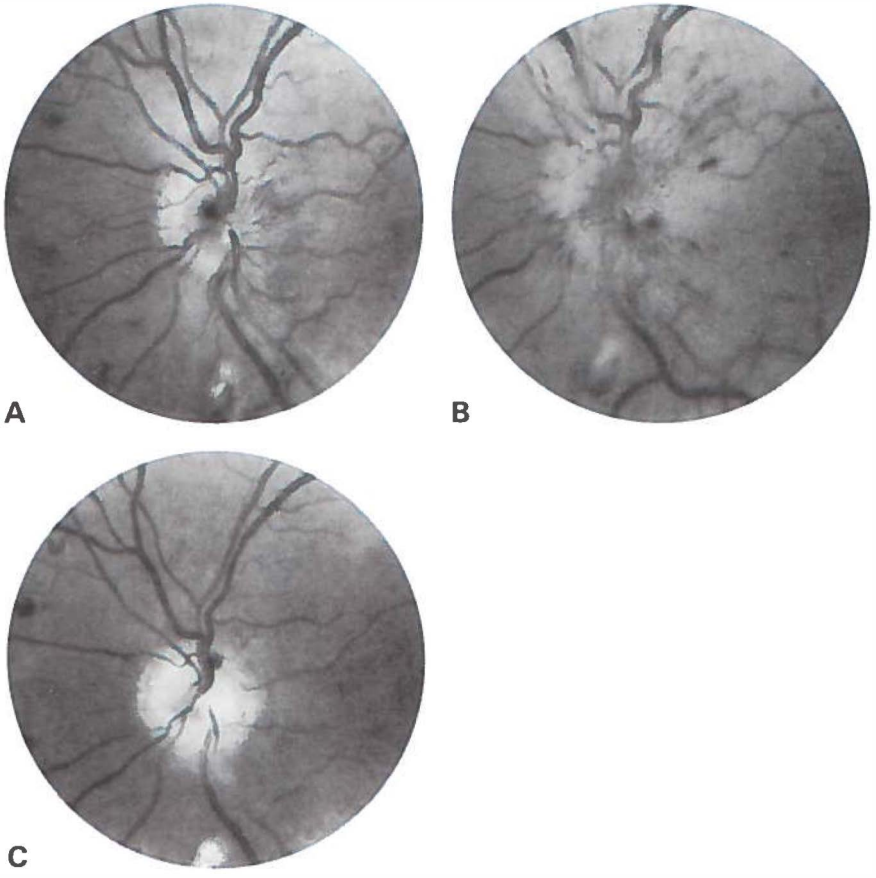


figures 3.5 A-C. Patient no. 35. Late phase angiograms of the right eye, macular area.

A, taken 2 months prior to CSII treatment.

B, after 6 months of CSII treatment. Cystoid macular edema had developed.

C, marked progression of cystoid macular edema after 8 months of CSII.



figures 3.6 A-C. Patient no. 34. Photographs of the left optic disc.

A, taken at commencement of CSII treatment. The optic disc shows radially oriented dilated capillaries.

B, after 4 weeks of CSII treatment a marked swelling of the optic disc and nerve fiber layer hemorrhages had developed.

C, six months after the start of CSII, optic disc edema has resolved. The optic disc became atrophic.

athy and scars of photocoagulation, so had to be classified as 6/6 (see definitions of retinopathy levels: chapter 2.3.2.). Panretinal photocoagulation was performed in both eyes of 3 patients (no. 16, 17 and 18) prior to CSII treatment. In 2 of them retinopathy remained stable throughout the year of treatment. Two months after the beginning of CSII however, a small vitreous hemorrhage occurred in one eye of patient no. 18. This subsequently cleared and additional photocoagulation was performed. Thereafter retinopathy remained stable.
As to the 2 cases (no. 9 and 12) that received no photocoagulation prior to CSII, retinal new vessels in both eyes of patient no. 12 showed progressive epiretinal growth. Photocoagulation had to be applied after 5 months of CSII. Thereafter retinopathy stabilized. The small new vessels on the optic disc of both eyes of patient no. 9 remained unchanged during the first 12 months of CSII treatment. A summary of the course of retinopathy in these 5 patients is given in table 3.7.

table 3.7. The course of proliferative retinopathy during the first year of CSII treatment.

proliferative retinopathy	no. of patients	progression	stable	comment
photocoagulation prior to CSII	3	1	2	1 patient: VH in one eye. After additional photocoagulation retinopathy stabilized.
no photocoagulation prior to CSII	2	1	1	1 patient: progressive growth of NVE. Retinopathy stable after photo-coagulation.
total	5	2	3	

VH: vitreous hemorrhage.
NVE: new vessels elsewhere.

Figure 3.7. presents the distribution of patients by retinopathy level before CSII and at the one-year examination.
Ten out of the 29 patients (35%) with level 1 to 6/<6 showed worsening of

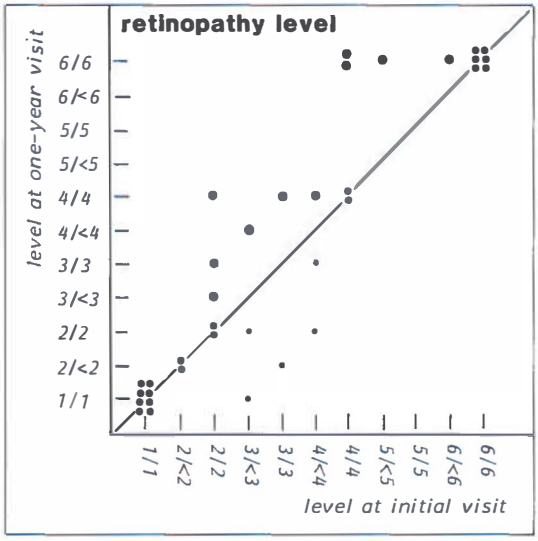


figure 3.7. Retinopathy level before and after one-year of CSII treatment.

Dots above the diagonal represent patients with progression of retinopathy. Dots below the diagonal represent patients with regression.

retinopathy after 1 year of CSII treatment. On the other hand, in 5 patients retinopathy improved. Improvement was observed only in patients with retinopathy level 4/<4 or less.
Of the 8 patients without retinopathy at the initial examination, none developed retinopathy during the observation period. In one patient (no. 10), with retinopathy level 3/<3, retinopathy regressed and was no longer visible after one year. Progression to the proliferative stage was observed only in patients with initial retinopathy level 4/4 or more.
Summarizing, during the first year of CSII treatment, the course of retinopathy was very unfavourable in 6 of our 35 patients. Four patients developed a severe proliferative retinopathy, 1 patient developed severe macular edema in both eyes and 1 patient developed optic atrophy in one eye due to ischemic optic neuropathy.

3.3. **Discussion**

There is experimental and clinical evidence that good blood sugar control

has a beneficial effect on diabetic vascular lesions (Tchobroutsky 1978). Initial case reports by Irsigler (1979), White et al. (1981) and Little (1981) utilizing CSII, suggested remarkable improvement of the fundus picture in patients with established diabetic retinopathy. Unfortunately none of these early observations have been confirmed in randomized one-year trials (Lauritzen et al. 1983, the Kroc Study Group 1984). These trials reported accelerated progression of retinopathy in the CSII groups, compared with the control for an observation period of 8-12 months. Deterioration consisted of increased numbers of soft exudates and intraretinal microvascular abnormalities. Dahl-Jørgensen et al. (1985) have designed a controlled prospective trial in patients with shorter durations of diabetes and less nonproliferative retinopathy than in the Steno Study and the Kroc Study. They observed a transient worsening of retinopathy in the CSII treated patients in the first 6 months. CSII did not accelerate progression of diabetic retinopathy in patients with no or minimal diabetic retinopathy (Olsen et al. 1985). The results of the present study are consistent with the published trials and are in accord with the clinical impression that a sudden improvement of blood glucose regulation can lead to a deterioration of retinopathy. In contrast to the observation of Dahl-Jørgensen et al. (1983), we observed no patients with transient proliferative retinopathy during CSII treatment.

As our patients were not matched with appropriate controls, no statement can be made about the findings of the present study as compared to the natural course of diabetic retinopathy.

However, a recent study of the natural history of diabetic retinopathy during conventional insulin treatment gives results of 2-year and 6-year follow-up examinations (Klein et al. 1984A). The patients in the study of Klein and the CSII treated patients of the present study were similar with respect to the type of diabetes, duration and age at diagnosis of diabetes and distribution of the levels of retinopathy. In both studies the same detailed protocol to document retinopathy status was used. This all justified a comparison between both studies. Of the 148 patients observed by Klein et al. after 2 years, 61 (41%) progressed, 6 (4%) of which developed a proliferative retinopathy. In the present study, after one year of CSII, 10 out of 29 patients (35%) showed progression of retinopathy and 4 out of 29 (14%) went into a proliferative retinopathy. Both studies suggest that the development of proliferative retinopathy is faster after rapid improvement of glucose control. This finding is in keeping with a report concerning progression of retinopathy after institution of good blood sugar regulation in children with poorly controlled diabetes (Daneman et al. 1981). The study reported the influence of improved diabetic control on retinopathy in 4 children with Mau-

riac's syndrome. In this syndrome (diabetic dwarfism) insulin-dependent children have a very bad blood sugar regulation causing hepatomegaly and growth failure. Three out of 4 children had a mild nonproliferative retinopathy; 1 child had no retinopathy. After improved diabetic control, by means of twice daily insulin injections, retinopathy progressed rapidly in all children, with severe proliferative changes in three. One child became blind in one eye as a result of a vitreous hemorrhage.

At present, an explanation for the unexpected progression of retinopathy can only be speculative. The pathogenesis of diabetic retinopathy is not well known but hypoxia and ischemia seem to be important factors in the development of proliferative retinopathy (Bresnick et al. 1976). Abrupt transition to near-normal blood glucose levels seems to induce the appearance of soft exudates and intraretinal microvascular abnormalities. Both lesions are associated with retinal hypoxia.

Retinal tissue is freely permeable to glucose and does not require insulin for glucose penetration. As a result of elevated ambient glucose concentration, excessive glucose is metabolized leading to intracellular accumulation of sorbitol and fructose in pericytes and endothelial cells (Tripathi et al. 1982). This may lead to cellular edema with impaired oxygen diffusion and hence anaerobic glycolysis increases. Rapid reduction of glycemia to normal levels sharply reduces the local concentration of glucose in the retina, thus depriving the hypoxic retina of nutritive elements.

Because of micro-angiopathic changes an impairment of vascular autoregulation is observed in patients with diabetic retinopathy (Sinclair et al. 1982). Ernest et al. (1983) suggest that acute hyperglycemia transiently increases retinal blood flow. The authors speculate that if patients with diabetic retinopathy were suddenly well controlled, the blood flow might actually decrease, resulting in areas of retinal ischemia and possible even infarction of the nerve fiber layer of the retina. This is clinically observed as soft exudates.

Possibly a slow gradual decrease in blood glucose level during the first months of CSII treatment can avoid worsening of retinopathy.

Hypoglycemia has also been mentioned as a possible cause of deterioration of retinopathy. However, we could not demonstrate a higher incidence of hypoglycemic episodes in the patients with severe worsening of retinopathy during CSII treatment as compared with the other patients.

Testa and co-workers (1985) have attempted to identify clinical predictors on retinopathy and its progression. Only patients with a mild nonproliferative diabetic retinopathy were included in the study. Low plasma glucose during CSII treatment was the best predictor of worsening of retinopathy.

In the present study, the 4 patients who developed a severe proliferative retinopathy during CSII treatment were characterized by a long duration of diabetes, a severe retinopathy at the onset of CSII treatment and the presence of proteinuria. Fundi of patients with these characteristics should be kept under close control with prompt recourse to photocoagulation therapy in case of any significant progression. In patients with proliferative retinopathy photocoagulation therapy should be completed prior to the beginning of CSII.

3.4. **Conclusions and recommendations**

- (Near)-normalization of blood glucose during treatment with CSII is ineffective in slowing down or arresting the progression of preproliferative and proliferative diabetic retinopathy over a one-year period.
- Rapid improvement of blood sugar control can have a harmful effect on established retinopathy.
- Intensified blood glucose control does not accelerate progression of diabetic retinopathy in patients with minimal retinopathy.
- During the first year of CSII treatment, patients with preproliferative lesions (soft exudates, intraretinal microvascular abnormalities, venous beading) should be kept under close ophthalmological control. If progression occurs photocoagulation is indicated.
- Panretinal photocoagulation should be carried out prior to CSII treatment in patients with proliferative retinopathy.

CHAPTER 4

THE INFLUENCE OF LONG-TERM CSII TREATMENT ON THE COURSE OF DIABETIC RETINOPATHY

4.1. **Patients**

The fundi of 24 type I diabetic patients, treated with CSII, were controlled during 24-60 months (mean 41.8 months). The group consisted of 6 males and 18 females. Of the 24 patients, 8 were observed during 2 years and 16 for more than 2 years. Of these 16 patients 13 were controlled for a period of 4 years or more. Only patients with good blood sugar regulation were selected for this follow-up study. Inclusion criteria were a HbA_1 level of $\leq 9\%$ in the second and subsequent years of CSII treatment and a mean blood glucose level of 3-8 mmol/l.
Of the 24 patients, 13 are also described in chapter 3, in which the course of

table 4.1. Patient data.

patient no.	age (yrs)/sex	duration of diabetes (yrs)	follow-up period (months)
1	30/M	16	60
2*	29/F	10	60
3*	30/F	8	60
4*	24/F	4	54
5	36/M	19	48
6	32/M	14	53
7	58/F	46	54
8	24/F	4	52
9	26/F	12	58
10	32/M	15	54
11*	25/F	11	51
12	26/M	5	48
13	31/F	16	48
14*	25/F	6	36
15*	27/F	2	35
16*	27/F	11	34
17*	23/F	13	26
18	29/F	13	28
19	28/F	5	24
20	29/F	9	24
21	21/F	5	24
22	24/F	9	25
23*	24/F	2	24
24	35/M	18	24

* pregnant in the period of observation.

retinopathy during the first year of CSII is studied. Six of the 24 patients are also described in chapter 5. They were observed during pregnancy. Apart from these 19 patients another 5 patients were included in this follow-up study. These 5 patients did not meet the inclusion criteria of the studies described in chapter 3 and 5. Three of them were photographed only once during pregnancy and of 2 patients mean blood glucose and HbA_1 levels prior to CSII were not known.
The mean age at diagnosis of diabetes was 17.6 years (range 14-25). The average age at the start of CSII treatment was 28.9 years (range 21-58). The average duration of diabetes at the onset of CSII treatment was 11.4 years (range 2-46). Age, sex, duration of diabetes and length of follow-up period are given in table 4.1.
Three patients (no. 5, 6 and 24) had a diabetic nephropathy (proteinuria $\geq$0.5 g/day).
Nine women became pregnant during the control period; seven of them delivered in the first year of CSII treatment, one patient (no. 11) was pregnant at the first year examination. Patient no. 4 was pregnant in the third year and patient no. 14 was pregnant in the first and third year of CSII treatment. No patient used other medication than insulin except patient no. 22, who used a contraceptive drug.

4.2. **Results**

4.2.1. *Results of glucose control*

In the second year of CSII treatment, 21 patients had a mean HbA_1 value of $\leq$ 9%. The remaining 3 patients had HbA_1 levels between 9.1 and 9.4%. The mean HbA_1 percentages during 5 years of CSII treatment are presented in table 4.2.

table 4.2. Mean HbA_1% during 5 years of CSII treatment.

year of CSII treatment	mean HbA_1% ± SD
1	8.2 ± 1.9
2	7.6 ± 1.0
3	7.3 ± 0.8
4	7.6 ± 0.7
5	7.2 ± 0.5

Mean HbA_1 levels of each patient were used to calculate the mean HbA_1 levels of the whole group. Individual data are given in table A-II (appendix).
Mean blood glucose levels also provide evidence of the long term effectiveness of CSII treatment. During CSII treatment mean blood glucose level of the whole group was 6.7 ± 1.0 mmol/l. Individual values are given in table A-III (appendix).
In the first year of CSII treatment patient no. 5 developed severe hypoglycemia. None of the patients had an episode of ketoacidosis.

4.2.2. *Ophthalmological results*

Patients characteristics prior to CSII, by retinopathy level in the worse eye, are given in table 4.3. Retinopathy level increases with duration of diabetes. The course of diabetic retinopathy during 2-5 years treatment with CSII is represented in table 4.4. and figure 4.1.

table 4.3. Patient characteristics before CSII by level of retinopathy in the eye with the more severe retinopathy.

retinopathy level	no. of patients	mean duration of diabetes (yrs)	mean age at diagnosis (yrs)
1	7	6.1	21.0
2	4	7.3	16.8
3	5	8.8	16.4
4	3	14.3	16.0
5	1	19.0	17.0
6	4	23.7	15.3

4.2.2.1. Patients with nonproliferative retinopathy at the start of the study

Progression of retinopathy occurred mostly within the first 12 months of treatment. In the first year, a proliferative retinopathy in both eyes (level 6/6) developed in 3 patients (no. 5, 6 and 24). Such a severe progression was not seen in the second and later years of treatment. Only one patient (no. 1) developed, after 2 years of CSII, some new vessels in the midperiphery of the retina of one eye (figs. 4.2 A-B). The small neovascularization showed

table 4.4. Retinopathy level during 2-5 years of CSII treatment.

patient no.	level of retinopathy before CSII	after 1 year CSII	after 2 years CSII	after 3 years CSII	after 4 years CSII	after 5 years CSII	comment
1	4/<4	4/4	6/<6	6/<6	6/<6	6/<6	– developed NVE after 2 yrs.
2	3/3	3/3	3/3	3/<3	3/<3	3/<3	
3	1/1	1/1	2/2	2/2	2/2	2/2	
4	2/2	2/2	2/2	2/2	3/<3		
5	5/<5	6/6	6/6	6/6	6/6		– developed PDR in both eyes in the first yr. VH in both eyes, despite PRP. One eye blind in the second yr.
6	4/4	6/6	6/6	6/6	6/6		– developed PDR in both eyes in the first yr. Regression after PRP.
7	6/6	6/6	6/6	6/6	6/6		– Progression of PDR in the second yr. Regression after PRP.
8	3/<3	1/1	2/<2	2/<2	2/<2		
9	1/1	1/1	1/1	2/<2	2/<2		
10	6/6	6/6	6/6	6/6	6/6		– Progression of PDR in the first yr. Regression after PRP.
11	3/<3	4/<4*	2/2	2/2	2/2		
12	1/1	1/1	2/<2	1/1	1/1		
13	6/6	6/6	6/6	6/6	6/6		– PRP prior to CSII. PDR remained stable.
14	3/<3	3/3	3/3	3/<3			
15	1/1	2/<2	1/1	1/1			
16	2/2	2/<2	2/<2	3/<3			
17	3/3	3/<3	3/3				
18	4/<4	2/2	2/<2				
19	1/1	1/1	1/1				
20	1/1	1/1	1/1				
21	2/<2	2/<2	2/<2				
22	2/2	3/<3	2/2				
23	1/1	1/1	1/1				
24	6/<6	6/6	6/6				– developed PDR in one eye and progression of PDR in the other eye during the first yr. VH in both eyes despite PRP.

* pregnant at ophthalmological examination.

NVE: neovascularization elsewhere.

PDR: proliferative diabetic retinopathy.

PRP: panretinal photocoagulation.

VH: vitreous hemorrhage.

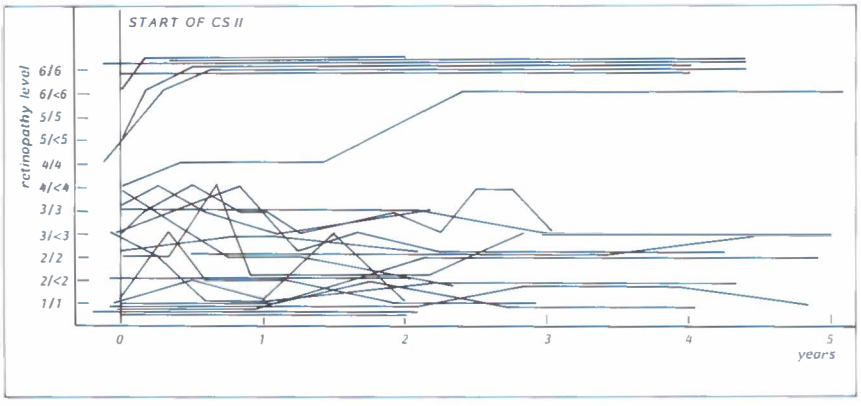
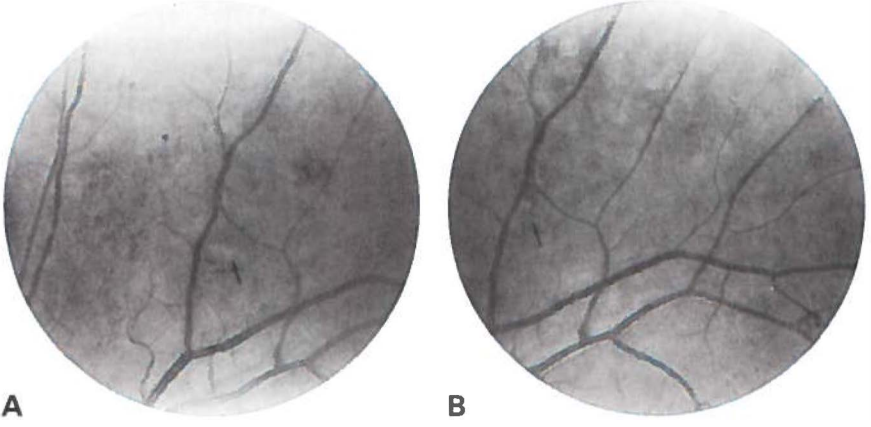


figure 4.1. The course of diabetic retinopathy during 2-5 years of CSII treatment.



figures 4.2 A-B. Patient no. 1. Fundusphotographs of the left eye, superior temporal region. Arrows point to corresponding areas of the retina.

A, taken after 5 months of CSII treatment. Note the soft exudate (arrow).

B, development of some retinal new vessels after 30 months of CSII treatment (arrow).

no progression during an observation period of 3 years and photocoagulation treatment was not necessary.
Less severe progression occurred more frequently, both in the first and the second year. Of the 20 patients with level 1 to level 5 before CSII, 7 (35%) progressed during the first year (fig. 4.3.). When excluding the 8 patients who were pregnant during the first year, progression of retinopathy at the one-year visit is seen in 4 out of the 12 remaining patients (33%). The equal percentage can be explained because at the one-year examination only one patient (no. 11) was still pregnant. During pregnancy progression of retinopathy occurs, after delivery however, regression is common (chapter 5). Figure 4.1. shows a temporary increase of retinopathy level in 6 patients during the first year; 5 of them being pregnant in this period.

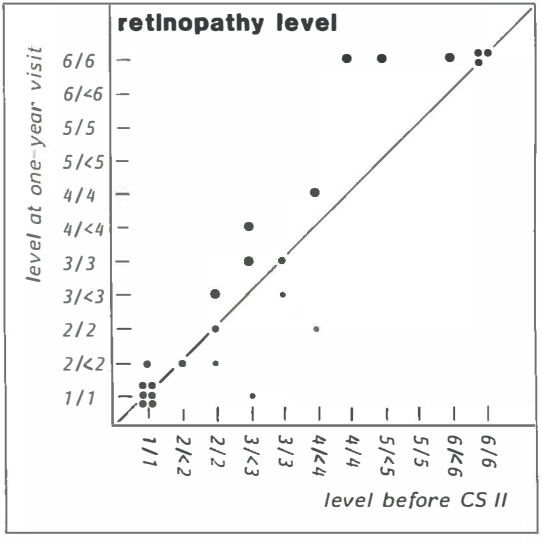


figure 4.3. Retinopathy level before and after one year of CSII treatment.

Dots above the diagonal represent patients whose retinopathy progressed. Dots below the diagonal represent patients with regression of retinopathy.

During the second year 5 out of 18 patients (28%) with level 1 to level 5, showed progression of retinopathy of one or more levels (fig. 4.4.). During the third, fourth and fifth year only minor changes in retinopathy were observed such as the appearance of microaneurysms and small intraretinal

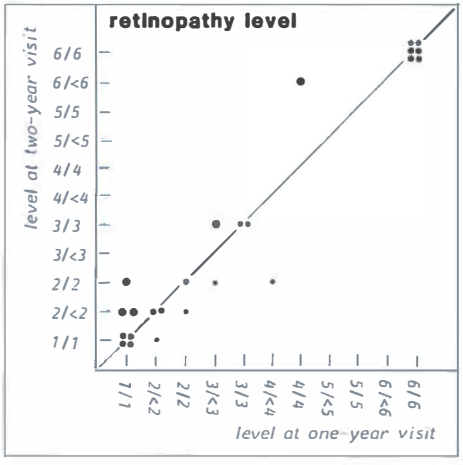


figure 4.4. Retinopathy level after after one and after two years of CSII treatment.

Dots above the diagonal represent patients with progression of retinopathy. Dots below the diagonal represent patients with regression.

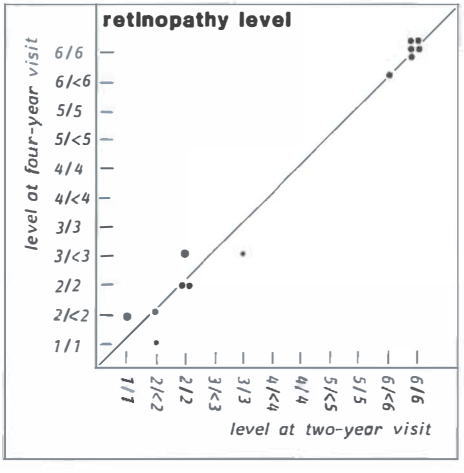


figure 4.5. Retinopathy level after two and after four years of CSII treatment.

Dots above the diagonal represent patients with progression of retinopathy. Dots below the diagonal represent patients with regression.

hemorrhages (fig. 4.5.). Only one patient (no. 14) showed a temporary progression in the third year during her pregnancy.
Regression of retinopathy was found only in patients with retinopathy level 4/<4 or less (table 4.4.). During the first 2 years of the study patient no. 18 showed regression of 4 levels (from level 4/<4 to level 2/<2).

4.2.2.2. Patients with proliferative retinopathy

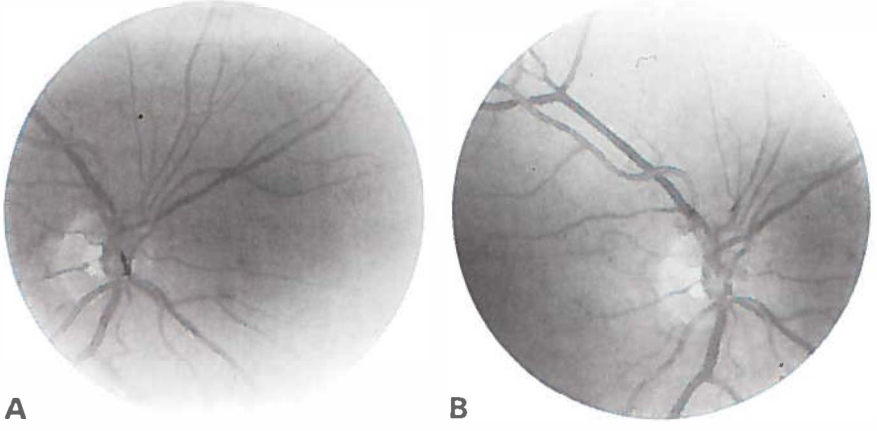
At the start of CSII 3 patients (no. 7, 10 and 13) had a proliferative retinopathy in both eyes; after one year it was observed in 3 more patients (no. 5, 6 and 24). Five of them had been treated by panretinal photocoagulation: one patient prior to CSII (no. 13) and 4 patients during the first year of CSII (no. 5, 6, 10 and 24). Proliferative retinopathy was untreated in one patient (no. 7). Photocoagulation was not performed in this patient because the small neovascularization on the optic disc remained unchanged during the first year of CSII treatment.
Proliferative retinopathy, once established, was not favourably influenced by CSII.
A summary of the course of proliferative retinopathy in the 6 patients is given in table 4.5.

table 4.5. The course of proliferative retinopathy during 2-5 years of CSII treatment.

proliferative retinopathy	no. of patients	progression	stable	comment
photocoagulation prior to CSII	1	–	1	
photocoagulation during the first year of CSII	4	2	2	recurrent VH in 2 patients
no photocoagulation treatment	1	1	–	regression after photocoagulation
total	6	3	3	

VH: vitreous hemorrhage.

Despite excellent blood sugar regulation and photocoagulation (either argon laser or xenon-arc and argon laser) 2 patients (no. 5 and 24) had recurrent vitreous hemorrhages in both eyes. In the second year of CSII, vitrectomy was performed in patient no. 5, because of an extensive vitreous hemorrhage. Thereafter retinopathy progressed further through neovascular glaucoma to phtisis. The second eye of this patient had several vitreous hemorrhages. After additional photocoagulation therapy, retinopathy stabilized 3.5 years after the start of CSII. The first vitreous hemorrhage in patient no. 24 occurred after one year of CSII treatment. During the second year, both eyes had several vitreous hemorrhages despite additional photocoagulation therapy. No regression of newly formed vessels could be observed during an observation period of 2 years.
Proliferative retinopathy was arrested in patient no. 6 and 10 after photocoagulation in the first year of CSII treatment. During the following 3 years, it remained stable. Patient no. 13 had received photocoagulation prior to CSII treatment. In this patient proliferative retinopathy remained unchanged during 5 years of CSII treatment.



figures 4.6 A-B. Patient no. 7. Photographs of the right optic disc.

A, taken 6 weeks prior to CSII treatment. A small neovascularization is present on the optic disc (arrow).

B, after 2 years of CSII treatment, showing progressive growth of the newly formed vessels on the optic disc.

Untreated proliferative retinopathy progressed and rubeosis iridis developed in both eyes of patient no. 7 during the second year of CSII treatment (figs. 4.6 A-B). After panretinal photocoagulation therapy, both retinopathy and rubeosis regressed and remained stable during the following 2 years.

4.3. **Discussion**

For several years investigators have tried to prove the hypothesis that normoglycemia will prevent or inhibit progression or may even ameliorate microvascular disease in diabetes. With the advent of CSII complemented by self-monitoring of blood glucose, it has become possible to achieve and maintain normoglycemia. During the first 12 months of CSII treatment however, an increase of retinopathy was observed in our patients (see chapter 3) and the same was found in several other studies (Lawson et al. 1982; Puklin et al. 1982; Lauritzen et al. and the Steno Study Group 1983; Kroc Study Group 1984). The Steno Study Group and the Kroc Study Group did a 2-year follow-up study.

In the Steno Study, 30 patients with advanced nonproliferative retinopathy were observed. The patients were randomized to conventional insulin treatment or to CSII. The mean HbA_1% was significantly lower in the CSII group (mean HbA_1% in the CSII group: 6.7 and in the conventionally treated group 8.3). After 2 years of treatment a marginally significant trend towards more frequent improvement of retinopathy was found among CSII treated patients as compared with conventionally treated patients (47% versus 14%). Four patients in the CSII group had developed a proliferative retinopathy after 2 years of treatment (2 during the first year). In the conventionally treated group 5 patients had a proliferative retinopathy after 2 years (1 during the first year) (Lauritzen et al. 1985).

The Kroc Study Group extended their randomized clinical trial from 8 to 24 months. Twenty-two patients were treated with CSII and 21 patients received conventional insulin therapy. For the 0-24-month study different levels of glycemic control were maintained for the CSII group (mean HbA_1%: 9.0) and for the conventionally treated group (mean HbA_1%: 10.8). During the second year of CSII treatment, the worsening of retinopathy in the CSII patients was no longer apparent. At 24 months the level of retinopathy of the conventionally treated patients was slightly worse than those managed by CSII, contrasting with the reported 8-month data (Kroc Study Group 1985 A+B). However, normoglycemia was not maintained during the sec-

ond year of CSII treatment. In the first 8 months mean HbA_1% was 8.0 (Kroc Study Group 1984). During the period of 0-24 months mean HbA_1% was 9.0. This may have affected the course of retinopathy.
Results of both the Steno Study and the Kroc Study suggest that the adverse effect of CSII on established diabetic retinopathy occurs mainly in the first year of CSII treatment.
Our own results are in accordance with those of the 2 studies mentioned above. In the first year of CSII 3 patients developed a severe proliferative retinopathy within 2-6 months leading to vitreous hemorrhages in 4 eyes and blindness in 1 eye. In the second and later years progression to such a severe proliferative retinopathy was not observed. Only one patient showed some small retinal new vessels in one eye after 2 years of treatment.
During the second year of CSII there is a greater tendency to improvement than to progression of nonproliferative retinopathy (Lauritzen et al. 1985; Kroc Study Group 1985: A+B). This contrasts with the course of proliferative retinopathy. Proliferative retinopathy deteriorated in 3 of our 6 patients; in 2 of them despite extensive photocoagulation therapy during the first year of treatment. It is clear that CSII offers no chance of improvement of retinopathy in these patients. It may well be that the damage in the late stages of retinopathy is too far advanced to be influenced by normalization of blood sugar control. Photocoagulation has definitely shown to be effective in most cases (Diabetic retinopathy study 1981A) and remains the only treatment available.
Whether long-term normoglycemia can prevent the development of diabetic retinopathy is unknown. A study lasting 10-15 years, on recently detected diabetics could answer this question.

4.4. **Conclusions**

- Rapid severe progression of established nonproliferative retinopathy (level 4/4 or more) during CSII is seen within the first year of treatment only.
- By the second and later years of CSII treatment there is a tendency towards stabilization of nonproliferative retinopathy.
- Normalization of blood sugar levels has no beneficial influence on the course of proliferative retinopathy. At present photocoagulation remains the only treatment available.

CHAPTER 5

THE INFLUENCE OF CSII TREATMENT ON THE COURSE OF DIABETIC RETINOPATHY DURING PREGNANCY

5.1. **Patients**

In this chapter the course of diabetic retinopathy is described during 37 pregnancies in 35 type I diabetic women treated with CSII. Duration of diabetes was 1-24 years (mean 12.3 years). The mean age at diagnosis of diabetes was 14.6 years (range 4-25). The mean age of the patients was 26.8 years (range 21-33). Two patients (no. 10 and no. 17) were pregnant twice during the study period. Diabetic retinopathy was studied during pregnancy and till 3 to 6 months after delivery. One patient (no. 5) was observed for only 5 months because of termination of pregnancy in the 16th week, owing to an anencephalic fetus.

All women had been referred for CSII treatment because they were either pregnant (19 patients) or were planning to become pregnant (18 patients). The latter group conceived within 1 month to 21 months after the start of CSII. Age, duration of diabetes and duration of CSII treatment prior to pregnancy are shown in table 5.1.

The study started in the first trimester of pregnancy. For the patients who planned to become pregnant the study started in the 6-month period prior to pregnancy. In 9 of the 18 patients planning to become pregnant, the start of the study coincided with the start of CSII treatment. The remaining 9 patients had been treated with CSII for more than 6 months before their pregnancy.

Hypertension and proteinura ($\geq$0.5 g/day) were present in 2 women (no. 7 and no. 12) before pregnancy; both were treated with antihypertensive drugs. None of the other women used any medication but insulin.

As a nonpregnant control group served 16 women of childbearing age with no or nonproliferative retinopathy. The course of retinopathy during their first year of CSII treatment is described in chapter 3. Both groups had similar clinical characteristics. Duration of diabetes in the control group was 3-22 years (mean 10.0 years). The mean age at diagnosis of diabetes was 16.2 years (range 6-27). The mean age of the women was 26.2 years (range 20-40).

5.2. **Results**

5.2.1. *Results of glucose control*

Near-normoglycemia during pregnancy could be achieved in all patients. The mean home blood glucose value was 6.0 $\pm$ 1.0 mmol/l. During pregnan-

table 5.1. Patient data.

patient no.	age (yrs)	duration of diabetes (yrs)	duration of CSII treatment prior to pregnancy (months)
1	33	24	21
2	29	14	1
3	30	13	12
4	28	6	8
5	21	11	2
6	25	19	4
7	25	14	14
8	21	11	6
9	25	11	7
10*	25	6	3
	27	8	24
11	24	2	3
12	23	17	20
13	27	11	4
14	24	6	5
15	27	23	20
16	32	21	1
17*	27	19	0
	29	21	18
18	28	24	0
19	23	13	0
20	30	12	0
21	29	13	0
22	22	7	0
23	31	10	0
24	24	11	0
25	31	16	0
26	26	5	0
27	24	1	0
28	27	13	0
29	32	20	0
30	27	2	0
31	30	10	0
32	25	8	0
33	27	5	0
34	26	15	0
35	29	12	0

* patient with 2 pregnancies during the study.

cy the mean HbA_1 level was 6.8 ± 0.5% (normal range 6-8.5%). The mean HbA_1 level on the day of delivery was 6.8 ± 0.1%.
Mean blood glucose values and mean HbA_1 levels during pregnancy of each patient are presented in table A-IV (appendix). None of the patients developed ketoacidosis. An episode of severe hypoglycemia occurred in 3 patients (no. 5, 24 and 30).

5.2.2. *Ophthalmological results*

Patient characteristics at first examination, by level of retinopathy in the worse eye, are given in table 5.2. The level of retinopathy generally increases with duration of diabetes.
The course of diabetic retinopathy during the study period is given in table 5.3. and figure 5.1.

table 5.2. Patient characteristics at first examination by level of retinopathy in the eye with the more severe retinopathy.

retinopathy level	no. of pregnancies	mean duration of diabetes (yrs)	mean age at diagnosis (yrs)
1	7	5.3	20.6
2	8	12.4	14.0
3	10	12.5	14.9
4	4	14.3	11.8
5	1	11.0	13.0
6	7	17.8	10.5

5.2.2.1. Patients with nonproliferative retinopathy at the start of the study

Retinopathy progressed during 20 out of 30 pregnancies (67%) in patients with nonproliferative retinopathy. One of these patients (no. 34) with retinopathy level 4/<4 at initial examination developed a proliferative retinopathy in one eye.
As is shown in figure 5.2., progression at the post partum examination as compared with the initial visit, was observed in only 9 of the 30 cases (30%). Thus in 11 cases progression during pregnancy was only temporary.

table 5.3. Level of retinopathy before and during pregnancy and at post partum examination, in CSII treated women.

patient no.	level of retinopathy				
	before pregnancy during/at start of CSII	during pregnancy			at post partum examination
		first trimester	second trimester	third trimester	
1	6/6	6/6	6/6	6/6	6/6
2	6/<6	6/<6	6/<6	6/<6	6/<6
3	2/2	2/2	2/2	4/<4	2/2
4	1/1	2/2	2/2	2/2	2/2
5	2/2	2/2	2/2		
6	4/<4	4/4	4/4	4/<4	3/<3
7	6/6	6/6	6/6	6/6	6/6
8	1/1	1/1	2/2	2/<2	2/<2
9	3/<3	4/<4	2/2	2/2	3/<3
10*	3/<3	4/<4	3/3	3/3	3/<3
	3/3	3/<3	4/<4	4/<4	3/<3
11	1/1	1/1	1/1	1/1	1/1
12	6/6	6/6	6/6	6/6	6/6
13	2/2	4/4	2/<2	2/<2	2/<2
14	2/2	3/<3	3/<3	3/<3	2/<2
15	6/6	6/6	6/6	6/6	6/6
16	6/6	6/6	6/6	6/6	6/6
17*		3/<3	4/<4	3/3	3/3
	3/3	2/2	2/2	4/<4	3/<3
18		2/2	2/2	2/<2	3/<3
19		3/3	4/<4	3/3	3/<3
20		6/6	6/6	6/6	6/6
21		2/2	3/3	2/2	2/2
22		4/4	4/<4	2/<2	2/2
23		1/1	1/1	1/1	1/1
24		5/5	6/<6	6/<6	6/<6
25		4/<4	4/<4	3/3	3/3
26		1/1	1/1	1/1	1/1
27		1/1	1/1	1/1	1/1
28		2/<2	2/2	2/2	3/<3
29		3/<3	4/<4	4/<4	4/<4
30		1/1	3/<3	2/<2	2/<2
31		3/<3	4/<4	2/2	2/2
32		2/<2	2/2	2/2	2/2
33		3/<3	3/<3	3/<3	2/<2
34		4/<4	4/4	6/<6	6/<6
35		3/<3	4/4	4/<4	2/2

* patient with 2 pregnancies.

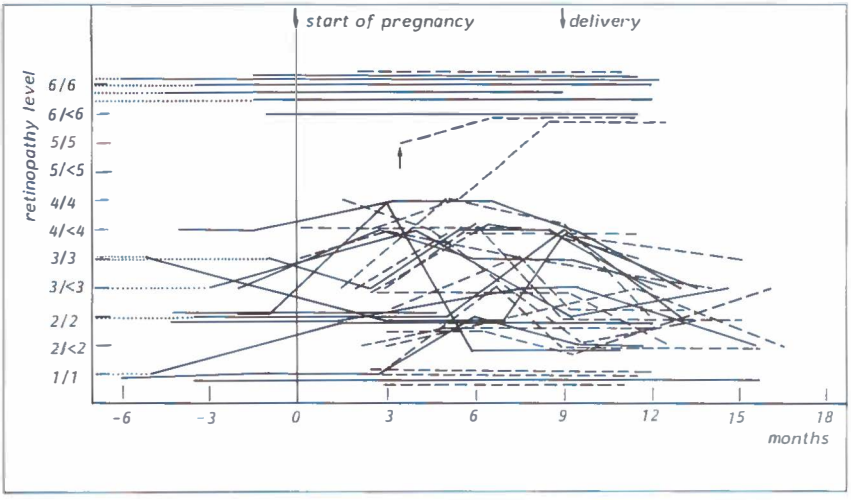


figure 5.1. The course of diabetic retinopathy during pregnancy and 3-6 months post partum in CSII treated patients.

——— CSII started prior to pregnancy.
– – – – – CSII started in first trimester.
..... treatment of CSII more than 6 months prior to pregnancy
→ this case changed to level 6/<6 because of photocoagulation treatment. Retinopathy remained stable.

In another 11 patients retinopathy had improved at post partum examination. In one patient (no. 22) retinopathy even regressed 5 levels during pregnancy (from 4/4 to 2/<2).
In figure 5.1. and 5.2. the patients, whose CSII treatment was started prior to pregnancy and in the first trimester of pregnancy respectively, are plotted in different ways. The reason for this was to check whether a disparity in the course of retinopathy exists between these two groups of patients.
As shown in table 5.4., there was no difference in the course of retinopathy during pregnancy between the two groups.
At post partum examination progression was seen mostly in the patients whose CSII was started in the first trimester: 7 out of 18 patients (39%) versus 2 out of 12 patients (17%) (fig. 5.2.).
The number of patients with progression during pregnancy (20 out of 30) is high. It is known that both CSII treatment, particularly during the first year (chapter 3; Lauritzen et al. 1983; the Kroc Study Group 1984; Dahl-Jørgen-

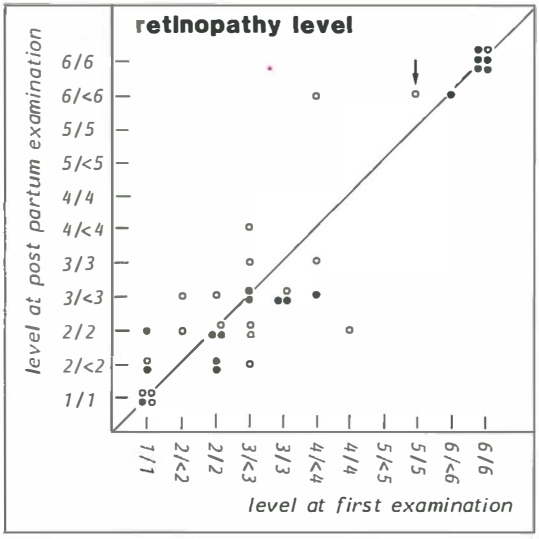


figure 5.2. Retinopathy level at first and post partum examination.

Marks above the diagonal represent patients with progression of retinopathy. Marks below the diagonal represent patients with regression.

→ This case changed to level 6/<6 because photocoagulation treatment in one eye. Retinopathy remained stable.

- CSII started prior to pregnancy.
- ◦ CSII started in the first trimester of pregnancy.

table 5.4. Progression of retinopathy during pregnancy in patients with nonproliferative retinopathy (level 1-5).

start of CSII	total number of patients	number of patients with progression of retinopathy
prior to pregnancy	12	10
in the first trimester of pregnancy	18	10
total	30	20

sen et al. 1985) and pregnancy (Cassar et al. 1978; Moloney et al. 1982) can influence the natural course of diabetic retinopathy. When comparing the change in retinopathy level of the women whose CSII treatment was started in the first trimester of pregnancy with that of nonpregnant women during the first year of their CSII treatment, it is possible to get an impression about the promoting factor causing the high number of patients with progression.

In 18 patients with no or nonproliferative retinopathy CSII was started in the first trimester of pregnancy. Patient no. 24 was excluded because of photocoagulation treatment during pregnancy. Characteristics of the 17 pregnant and the 16 control patients by level of retinopathy in the worse eye at first examination are given in table 5.5. It will be seen that these two groups are comparable.

table 5.5. Characteristics of pregnant and nonpregnant control patients by level of retinopathy in the worse eye, at first examination.

retinopathy level	number of patients		mean duration of diabetes (yrs)	
	control N=16	pregnant N=17	control	pregnant
1	5	4	6.2	4.5
2	3	4	6.0	14.5
3	4	6	10.5	13.2
4	4	3	17.5	12.7
5	–	–	–	–

At the end of the first year of CSII treatment retinopathy had progressed in 3 out of the 16 control patients (19%).

Figure 5.3. shows the course of nonproliferative retinopathy after the first 3, 6 and 9 months of CSII treatment in 17 pregnant and 16 nonpregnant control patients.

The figure clearly demonstrates that most progression occurred in the pregnant patients within the first 3 months of CSII treatment. Thereafter retinopathy regressed and no difference between pregnant and nonpregnant patients can be demonstrated after 9 months of CSII treatment. The difference in number of patients with progression after 3 months of CSII treat-

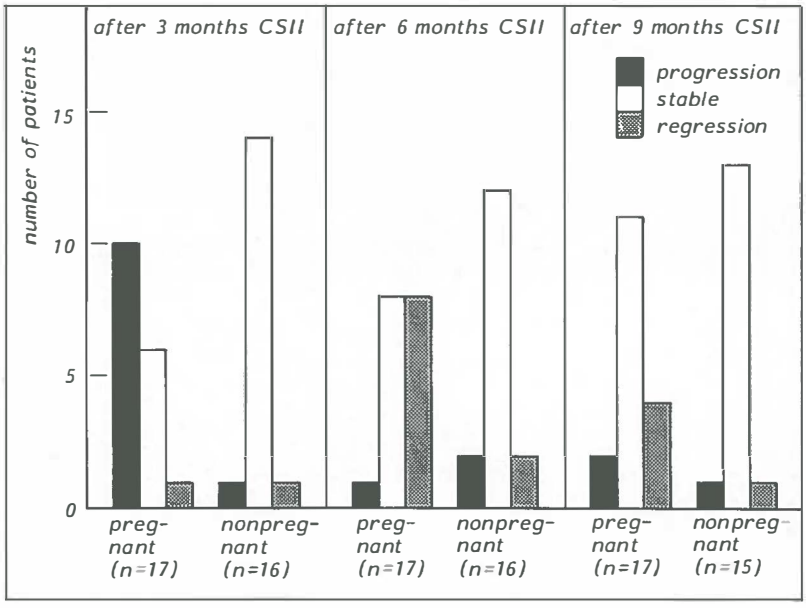
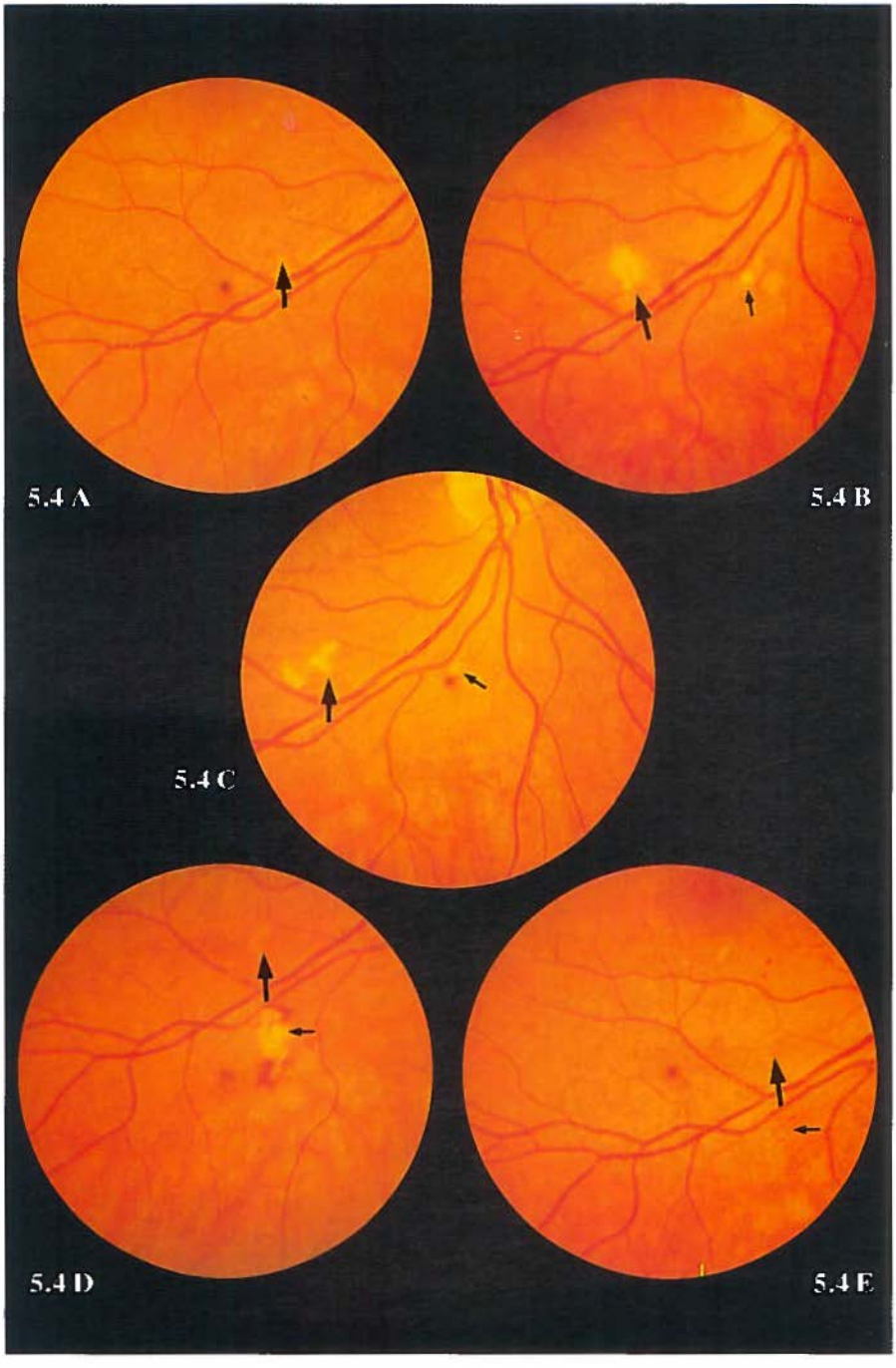


figure 5.3. Changes in retinopathy in pregnant and control patients during the first 9 months of CSII treatment.

ment between the pregnant (59%) and the control women (6.3%) is significant (chi-square test: $P<0.02$). The high percentage of progression of retinopathy during pregnancy is thus caused mostly by pregnancy itself. The institution of CSII treatment seems to be a less important factor.
The main lesions indicative for progression during pregnancy were soft exudates. Soft exudates developed during 13 out of 30 pregnancies (43%) (patient no. 3, 6, 9, 13, 19, 29, 31, 34, 35 and during both pregnancies of patient no. 10 and 17). In most cases they were noted in the second trimester of pregnancy (7 patients). Sometimes they appeared in the first (3 patients) or in the third trimester (3 patients). No new soft exudates developed after delivery. (figs. 5.4 A-E) (table 5.6.).
In 10 of the 13 patients the appearance of soft exudates came within the first year of CSII treatment. It was striking that they did not develop in patients with no or minimal retinopathy (level 1/1 and 2/<2).
Two out of the 16 control patients (13%) developed soft exudates during an observation period of 12 months.


5.4 A
5.4 B
5.4 C
5.4 D
5.4 E

figures 5.4 A-E. Patient no. 2. Fundusphotographs of the right eye, inferior temporal region. Arrows indicate corresponding points.

A, taken after 2 months of CSII treatment in the fourth week of pregnancy. A small soft exudate is present (arrow).

B, taken 2 months later. The soft exudate has increased and a new soft exudate has developed.

C, one month later, the soft exudates are in regression.

D, taken one month later. The soft exudates have disappeared but a new one with small intraretinal hemorrhages has developed (arrow).

E, 4 weeks later, in the sixth month of pregnancy all soft exudates have disappeared.

table 5.6. Presence of soft exudates.

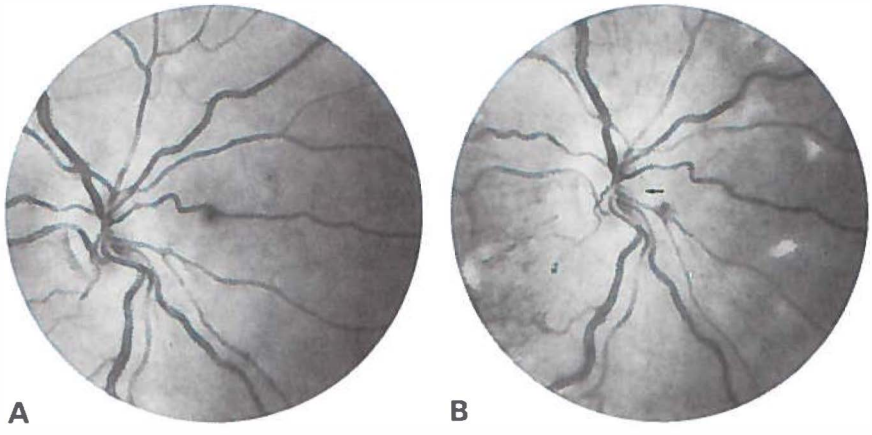
start of CSII	number of patients with soft exudates	during pregnancy trimester			at post partum visit
		1	2	3	
prior to pregnancy	7	2	4	1	–
in the first trimester of pregnancy	6	1	3	2	2
total	13	3	7	3	2

Of the remaining 7 patients who showed progression of retinopathy during pregnancy 4 had an increase in microaneurysms and hemorrhages and 3 patients developed some microaneurysms only.

Three histories are mentioned because of the special course.

In patient no. 34 retinopathy deteriorated severely. At first examination, in the first trimester of pregnancy, some soft exudates were present in one eye

(level 4/<4). In the second trimester there was a marked increase of soft exudates and flame-shaped hemorrhages had developed. In the third trimester some small newly formed vessels were present on the optic disc of one eye (level 6/<6) (figs. 5.5 A-B).



figures 5.5 A-B. Patient no. 34. Fundusphotographs of the right eye.

A, taken before the start of CSII treatment in the eighth week of pregnancy.

B, after 6 months of CSII treatment, some small newly formed vessels on the disc (arrow), soft exudates and flame-shaped hemorrhages have developed.

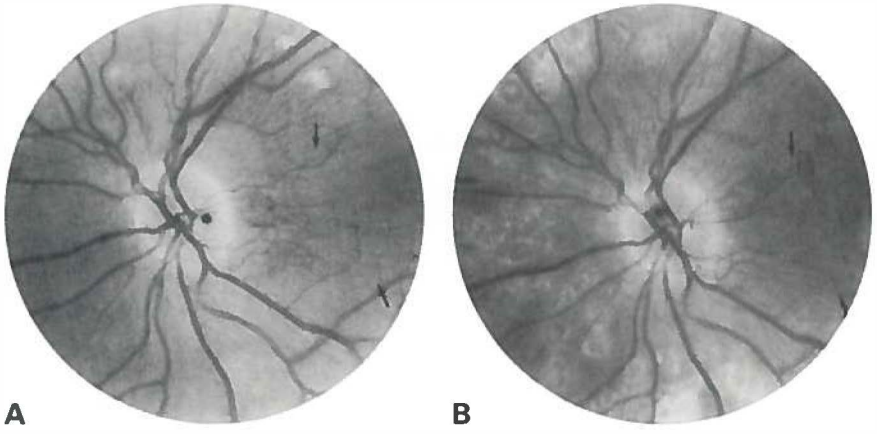
In patient no. 24 retinopathy level increased during pregnancy from 5/5 to 6/<6. At initial visit at the end of the first trimester of pregnancy, a severe preproliferative retinopathy was observed. During the second trimester prophylactic xenon-arc photocoagulation was performed in one eye. In the following period retinopathy in both eyes remained stable. No progression towards proliferative retinopathy was observed. Because of scars of photocoagulation and not on account of progression of retinopathy this patient had to be classified as level 6/<6 (see definitions of retinopathy levels: chapter 2.3.2.).

In patient no. 22 retinopathy regressed 5 levels during pregnancy. At first examination in the sixth week of pregnancy soft exudates were present in

both eyes. CSII was started 6 weeks prior to the first ophthalmological examination. During pregnancy retinopathy gradually ameliorated. Three weeks after delivery only a few microaneurysms in one eye were present. Four months after childbirth some microaneurysms were present in both eyes (level 2/2).

5.2.2.2. Patients with proliferative retinopathy at the start of the study

Of our patients, 6 had a proliferative retinopathy in both eyes (no. 1, 7, 12, 15, 16 and 20) and one had proliferations in one eye (no. 2). Five patients had received panretinal photocoagulation therapy in both eyes prior to pregnancy (no. 1, 7, 12, 15 and 20). Two patients were untreated when they became pregnant (no. 2 and 16). In these 2 patients proliferative retinopathy was diagnosed at their initial examination.



figures 5.6 A-B. Patient no. 2. Fundusphotographs of the left optic disc. Arrows point to corresponding areas.

A, taken after 2 months of CSII treatment in the fourth week of pregnancy. Newly formed vessels on the optic disc are present.

B, shows clear progression of the newly formed vessels on the disc after 4 months of CSII. Photocoagulation treatment was started.

In the 5 patients treated with photocoagulation, one vitreous hemorrhage occurred during pregnancy (patient no. 7). After additional photocoagulation retinopathy stabilized. The remaining 4 patients showed no or little change in the fundus picture throughout pregnancy. Some soft exudates appeared between the scars of photocoagulation in one patient (no. 20), which disappeared after delivery.
Both untreated patients showed progression of proliferative retinopathy during pregnancy. The new vessels in the midperiphery of the retina in both eyes of patient no. 16, showed a slow, epiretinal growth. In patient no. 2 a progressive growth of newly formed vessels on the optic disc of one eye was observed in the first trimester (figs. 5.6 A-B). Extensive argon laser treatment was then performed resulting in regression of the new vessels; retinopathy remained stable during the following 6 months. The second eye of this patient showed no change in retinopathy during pregnancy (level 4). A summary of the course of retinopathy in these 7 patients is given in table 5.7.

table 5.7. The course of proliferative retinopathy during pregnancy in CSII treated women.

proliferative retinopathy	no. of patients	progression	stable	comment
photocoagulation prior to pregnancy	5	1	4	1 patient: VH in one eye. After additional photocoagulation retinopathy stabilized
no photocoagulation treatment	2	2	–	1 patient: slow growth of NVE in both eyes. 1 patient: progressive growth of NVD in one eye
total	7	3	4	

VH: vitreous hemorrhage.
NVE: new vessels elsewhere.
NVD: new vessels on the disc.

5.2.3. Outcome of pregnancy

Diabetic pregnancy is associated with increased obstetrical complications and poorer fetal outcome. The pregnancy outcome of 147 conventionally treated diabetic women was analyzed by Kitzmiller et al. (1978). They found 9% major congenital anomalies in their infants. Several investigators reported an increased risk of congenital malformations in infants born to mothers with long duration of diabetes (more than 20 years) and the presence of vascular complications: White classes D, F and R (White 1978). In these women percentages of 13% infants with major congenital malformations are reported (Mølsted-Pedersen, 1985). The malformation rate for infants of non-diabetic women is 1.5% (Fuhrmann et al. 1983).
In the present study there was one case of (unexplained) intrauterine death during the 37th week of pregnancy; one infant died soon after birth due to a complex heart malformation. In one woman pregnancy was terminated because of anencephalus and one woman had an infant with spina bifida. Of the 4 diabetics (11%) who had these children, one woman had no retinopathy, one had only some microaneurysms, one had a moderate nonproliferative retinopathy and one had a severe proliferative retinopathy. In 2 out of the 4 cases CSII was started prior to pregnancy.

5.3. **Discussion**

The risk of progression of retinopathy during pregnancy is reported to be high, however regression after delivery is common (Cassar et al. 1978; Horvat et al. 1980; Moloney et al. 1982; Dibble et al. 1982). All authors describe progression of retinopathy in both nonproliferative and proliferative cases, although the proliferative cases clearly present the greatest hazard (see chapter 1.1.4.). Because different definitions and classifications have been used by these authors, it is not easy to compare their results with those of the present study.
That photocoagulation, performed prior to pregnancy in women with proliferative retinopathy, improves their prognosis has been reported by Cassar et al. 1978 and Gerke et al. 1982.
We also found that pregnancy influences the course of retinopathy unfavourably. Retinopathy progressed despite good blood sugar regulation in 67% of the patients who started with nonproliferative retinopathy. Striking was the high percentage of patients who developed soft exudates. They were the most prominent cause of deterioration in our patients and appeared in 13 of the 30 patients (43%) with nonproliferative retinopathy.

In a controlled study of Moloney et al. (1982) soft exudates were found in 29% of their conventionally treated pregnant patients and in 0% of the non-pregnant control group. Of the 17 women in the present study, with no or nonproliferative retinopathy and in which CSII was started in the first trimester of pregnancy 6 (35%) developed soft exudates. Of the 16 control patients 2 (13%) developed soft exudates during the first year of CSII treatment. Since Moloney and co-workers did not specify the broad range of nonproliferative retinopathy it is difficult to compare their figures with those of the present study.
The difference in progression found at the postpartum examination between the women who started with CSII prior to pregnancy as compared with those who started with it in the first trimester - 17% versus 39% - (fig. 5.2.) is probably caused by the difference in duration of CSII treatment between both groups. Mean duration of CSII treatment in the patients in which CSII was started in the first trimester of pregnancy was 10 months, at the post partum examination. In patients in which CSII was started prior to pregnancy the mean duration of CSII at the final examination was 22 months. Since progression of retinopathy was observed in 19% of the non-pregnant control patients at the end of the first year of CSII treatment it is likely, that the higher percentage of progression at final examination in the patients in which CSII was started in the first trimester, was caused by the shorter duration of CSII treatment in these patients. In the second and later years of CSII treatment there is a tendency towards stabilization of nonproliferative retinopathy (chapter 4). This can explain the lower percentage of progression in the group in which CSII was started prior to pregnancy.
An association between progression of retinopathy and hypertension or hypoglycemia has not been found. No severe proliferative changes as reported in nonpregnant, CSII treated patients with preproliferative and proliferative retinopathy (chapter 3; Lawson et al. 1982; Ballegooie et al. 1984A) were observed in the pregnant women. However, 5 out of our 7 pregnant patients with proliferative retinopathy had received photocoagulation therapy prior to pregnancy.

5.4. **Conclusions and recommendations**

- Pregnancy has an unfavourable, though temporary, effect on the course of nonproliferative diabetic retinopathy in CSII treated women.
- The main lesions indicative for progression of retinopathy during pregnancy are soft exudates.

- Pregnant CSII treated patients with preproliferative retinopathy should be examined every month, starting early in pregnancy. When neovascularizations develop photocoagulation treatment should be performed.
- In patients with proliferative diabetic retinopathy, who intend to become pregnant, panretinal photocoagulation should be performed prior to the institution of CSII treatment.
- In women with proliferative retinopathy, already pregnant and starting with CSII, photocoagulation should be carried out as soon as possible.

SUMMARY

Summary

The aim of this prospective study was to investigate the effect of normalization of blood sugar regulation by continuous subcutaneous insulin infusion (CSII) on the course of diabetic retinopathy in insulin-dependent (type I) diabetic patients.

At the start of the study the following questions were formulated:

- what is the influence of improved blood sugar control on diabetic retinopathy shortly after the initiation of CSII? (chapter 3).
- what is the long-term influence of CSII on diabetic retinopathy? (chapter 4).
- what is the effect of CSII treatment on diabetic retinopathy during pregnancy? (chapter 5).

The development of diabetic retinopathy is strongly related to the duration of diabetes mellitus. To what extent good blood sugar control influences the development of diabetic retinopathy has never been clearly established. This is not remarkable, because with conventional treatment - diet and insulin injections - normoglycemia is difficult to maintain in type I diabetic patients. This became possible only recently with the advent of continuous subcutaneous insulin infusion (CSII). By way of a portable miniature syringe pump, insulin is administered continuously, bolus injections being added before the start of a meal. Blood glucose levels become normalized or almost normalized, even in cases where conventional therapy fails to induce improvement.

In chapter 1 a review of literature is given on the natural history of diabetic retinopathy, the treatment of proliferative retinopathy and the effect of metabolic control on the course of diabetic retinopathy. The first case reports concerning the effect of CSII on diabetic retinopathy showed remarkable improvement of the fundus picture. However, randomized one-year trials could not demonstrate these beneficial effects. On the contrary accelerated progression of retinopathy was found in some cases. The last section of chapter 1 deals with the classification of diabetic retinopathy as has been used in the present study.

In chapter 2 the patients are described, as well as the methods of glucose control and of ophthalmological examination.

The results, in 35 patients, of the effect of one year improved glycemic control on diabetic retinopathy are presented in chapter 3. Of the 29 patients with no or nonproliferative retinopathy at the start of the study 10 (35%) showed progression of retinopathy. Four of these 10 patients developed a severe proliferative retinopathy within 2 to 6 months. In 6 patients soft exu-

dates appeared during CSII treatment. In 2 other patients the course of retinopathy was unfavourable for different reasons. On the other hand, in 5 patients retinopathy improved, but this happened only in patients with mild retinopathy. Patients with a proliferative retinopathy at the start of the study fared worse: in 2 out of 5 of them retinopathy progressed and photocoagulation treatment had to be performed. The results of the study show that (near)-normalization of blood glucose levels by means of CSII does not prevent the progression of diabetic retinopathy. A sudden improvement of blood glucose levels can even lead to a severe deterioration of the fundus picture.

Chapter 4 describes the long-term influence of CSII on the course of diabetic retinopathy. In all 24 patients (near)-normoglycemia could be maintained during 2-5 years. A severe progression as observed in the first year of CSII was not seen in the second and later years. Only one of the patients developed a few new vessels during the second year of CSII treatment. Progression of nonproliferative retinopathy during the second year occurred in 5 out of 18 patients (28%). During the third, fourth and fifth year only minor changes were observed. After 2 years of CSII there is a greater tendency to improvement than to progression of nonproliferative retinopathy. This contrasts with the course of proliferative retinopathy. Proliferative retinopathy deteriorated during the second and later years in 3 out of 6 patients, in 2 of them despite extensive photocoagulation therapy.

In chapter 5 the effect of CSII on the course of diabetic retinopathy in 35 pregnant patients during 37 pregnancies is discussed. Nonproliferative retinopathy progressed, despite excellent blood sugar regulation during 67% of the pregnancies. In half of the cases progression was only temporary. The main lesions indicative for progression were soft exudates, but one of the patients progressed to proliferative retinopathy. The high percentage of progression seems to be caused mostly by pregnancy itself and in a less degree by the institution of CSII treatment. In 3 out of 7 patients with proliferative retinopathy a deterioration was observed. It remained stable in 4 patients who had received photocoagulation treatment prior to pregnancy. In patients with proliferative retinopathy, who intend to become pregnant, photocoagulation should be performed prior to the institution of CSII treatment.

SAMENVATTING

Samenvatting

De doelstelling van dit prospectieve onderzoek was na te gaan of normalisatie van de bloedsuikerregulatie met behulp van continue subcutane insuline infusie (CSII) de progressie van diabetische retinopathie bij patiënten met een insuline-afhankelijke diabetes mellitus (type I) kan tegenhouden of vertragen.
Bij het begin van het onderzoek werden de volgende vragen geformuleerd:
- wat is de invloed van een scherpe bloedsuikerregeling op diabetische retinopathie na overschakeling van conventionele insuline therapie op CSII? (hoofdstuk 3).
- wat is op de lange duur de invloed van CSII op diabetische retinopathie? (hoofdstuk 4).
- wat is de invloed van CSII op diabetische retinopathie tijdens de zwangerschap? (hoofdstuk 5).

Het ontstaan van diabetische retinopathie lijkt duidelijk mede bepaald te worden door de duur van de diabetes mellitus. Minder eenduidig is de literatuur over de vraag of de kwaliteit van de bloedsuikerregulatie invloed heeft op het ontstaan en het verloop van diabetische retinopathie. Het antwoord hierop is moeilijk te geven omdat het bij type I diabeten meestal onmogelijk is met de conventionele middelen - dieet en insuline injecties - gedurende het gehele etmaal normoglycemie te handhaven. Het normale insuline-secretiepatroon is tegenwoordig beter te benaderen met behulp van CSII. Via een draagbaar pompje krijgt de patiënt continu een kleine hoeveelheid insuline toegediend en bovendien een extra hoeveelheid voor de maaltijd. Hiermee lukt het meestal nagenoeg normale bloedsuikerspiegels te bereiken en te handhaven.
In het eerste deel van hoofdstuk 1 wordt een literatuuroverzicht gegeven van het natuurlijke beloop van diabetische retinopathie, de behandeling van proliferatieve retinopathie en de invloed van de bloedsuikerregulatie op diabetische retinopathie. Aanvankelijk waren de berichten over het effect van een scherpe bloedsuikerregeling met behulp van CSII op het verloop van diabetische retinopathie erg gunstig. Latere, grotere studies konden deze positieve resultaten niet bevestigen. Integendeel, in enkele gevallen werd, kort na de instelling op CSII een toeneming van de retinopathie waargenomen. In de laatste paragraaf van hoofdstuk 1 wordt ingegaan op de classificatie van diabetische retinopathie welke in dit onderzoek gebruikt werd.
In hoofdstuk 2 worden de patiënten beschreven die deelnamen aan het on-

derzoek, en verder de toegepaste methoden van bloedsuikerregulatie en het oogheelkundig onderzoek.
In hoofdstuk 3 worden de resultaten weergegeven van het effect van 1 jaar behandeling met CSII op diabetische retinopathie. Vijfendertig patiënten waren bij dit onderzoek betrokken. Na overschakeling op CSII daalden de gemiddelde bloedsuikerspiegel en het gemiddelde percentage geglycosyleerde hemoglobine (HbA_1) tot normale waarden. Van de 29 patiënten zonder of met een niet-proliferatieve retinopathie toonden er 10 (35%) een toeneming van de afwijkingen. Vier van deze 10 patiënten ontwikkelden binnen 2-6 maanden na de instelling op CSII zelfs een zeer ernstige proliferatieve retinopathie. Bij 6 patiënten nam de retinopathie in mindere mate toe; er ontwikkelden zich bij hen zachte exsudaten. Bij 2 van de patiënten met een niet-proliferatieve retinopathie traden andere ernstige afwijkingen op, waardoor de visus aanzienlijk slechter werd (een patiënt ontwikkelde een dubbelzijdig cystoid maculaoedeem; een patiënt kreeg een opticus atrofie na een ischaemische neuropathie). Daar tegenover stonden 5 patiënten bij wie de retinopathie verbeterde. Dit gebeurde echter alleen in het beginstadium van de retinopathie. Bij de 5 patiënten die al een proliferatieve retinopathie hadden bij het begin van de CSII behandeling trad nimmer verbetering van de retinopathie op. Bij 2 van hen werd de toestand slechter. Uit de resultaten blijkt dat normalisatie van het bloedsuikergehalte met behulp van CSII, de progressie van diabetische retinopathie niet altijd tegenhoudt. Kort na instelling op CSII kan, afhankelijk van het beginstadium, het fundusbeeld zelfs aanzienlijk slechter worden. De risico's zijn het geringst als de retinopathie, bij overschakeling op CSII, niet of nauwelijks aanwezig is.
In hoofdstuk 4 wordt het effect beschreven van CSII op het verloop van diabetische retinopathie over een periode van 2-5 jaar. Alle 24 patiënten handhaafden normale bloedsuikerwaarden. Ernstige progressie zoals gezien werd in het eerste jaar CSII behandeling trad in het tweede en volgende jaren niet meer op. Slechts 1 patiënt ontwikkelde een zeer kleine neovascularisatie in het tweede jaar van de behandeling. Geringe progressie van niet-proliferatieve retinopathie trad in het tweede jaar op bij 28% van de patiënten. In het derde, vierde en vijfde jaar traden slechts minimale veranderingen op. Na het eerste jaar CSII behandeling lijkt er een tendens te zijn tot stabilisatie van niet-proliferatieve retinopathie. Reeds aanwezige proliferatieve retinopathie werd niet gunstig beïnvloed door de goede bloedsuikerregulatie. Ook ná het eerste jaar nam de progressie bij 3 van de 6 patiënten toe; bij 2 van hen in de vorm van recidiverende glasvochtbloedingen ondanks panretinale fotocoagulatie.

Hoofdstuk 5 beschrijft de invloed van CSII op diabetische retinopathie tijdens de zwangerschap. Vijfendertig vrouwen werden tijdens 37 zwangerschappen gevolgd. Ondanks een optimale bloedsuikerregulatie trad in 67% van de zwangerschappen progressie van niet-proliferatieve retinopathie op. De progressie uitte zich voornamelijk in de vorm van zachte exsudaten. In de helft van de gevallen was de verslechtering van de retinopathie tijdelijk. Een patiënte ontwikkelde een proliferatieve retinopathie. De progressie lijkt hoofdzakelijk veroorzaakt te worden door de zwangerschap zelf. De instelling op CSII lijkt slechts een beperkte bijdrage te leveren tot de toeneming van de retinopathie. Bij 3 van de 7 patiënten met een proliferatieve retinopathie verslechterde de oogheelkundige situatie. Vier patiënten die vóór de zwangerschap fotocoagulatie behandeling gehad hadden toonden echter geen verandering in het fundusbeeld. Bij patiënten met een proliferatieve retinopathie en zwangerschapswens moet voor de instelling op CSII, fotocoagulatie verricht worden.

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APPENDIX

table A-I. Mean blood glucose (MBG) values (± SD) and HbA_1% before and during CSII.

patient no.	MBG (mmol/l) before CSII	MBG (mmol/l) during 0-12 months CSII	HbA_1% before CSII	HbA_1% after 6 months CSII	HbA_1% after 12 months CSII
1	20.3 ± 6.9	11.8 ± 3.7	13.2	9.8	9.6
2	10.9 ± 3.7	5.1 ± 2.2	13.0	6.1	8.7
3	12.2 ± 5.1	9.0 ± 4.7	11.6	8.0	8.5
4	13.9 ± 3.5	6.1 ± 2.2	10.7	8.2	8.8
5	11.5 ± 5.3	5.0 ± 1.8	16.9	8.3	9.9
6	17.5 ± 6.8	9.4 ± 3.8	11.8	8.2	8.3
7	14.4 ± 3.5	7.4 ± 3.6	12.1	8.3	9.6
8	10.6 ± 3.1	5.7 ± 2.7	12.2	7.2	7.9
9	14.7 ± 5.6	6.5 ± 4.9	10.4	6.9	8.5
10	18.0 ± 6.4	6.0 ± 2.2	14.4	8.3	8.2
11	11.0 ± 3.9	5.9 ± 2.5	11.8	8.9	6.8
12	14.7 ± 5.2	4.7 ± 1.6	12.9	6.8	7.6
13	7.9 ± 3.0	6.8 ± 2.9	9.7	8.8	7.8
14	11.4 ± 4.6	7.8 ± 0.9	10.0	7.5	6.7
15	12.7 ± 9.5	9.1 ± 4.1	10.2	9.6	7.7
16	13.6 ± 4.9	7.2 ± 2.0	9.8	7.9	6.3
17	9.8 ± 1.8	5.7 ± 4.0	9.6	6.9	7.7
18	11.0 ± 3.4	7.1 ± 1.2	9.1	7.3	7.7
19	8.0 ± 3.6	6.4 ± 4.5	8.8	6.9	6.8
20	12.4 ± 2.3	7.9 ± 1.2	7.6	8.8	7.9
21	7.9 ± 5.4	6.9 ± 3.1	6.7	6.3	6.6
22	11.4 ± 3.2	8.8 ± 1.1	9.8	9.6	7.9
23	13.6 ± 5.4	6.2 ± 5.8	8.4	7.5	8.5
24	13.9 ± 8.5	6.5 ± 8.6	10.7	6.3	6.5
25	9.7 ± 0.9	7.2 ± 1.6	9.5	6.0	6.8
26	7.9 ± 2.5	8.3 ± 2.8	8.1	7.5	5.7
27	8.9 ± 4.5	11.5 ± 2.6	9.3	7.1	8.0
28	7.9 ± 4.0	11.6 ± 3.2	9.0	7.6	9.2
29	10.0 ± 2.1	8.2 ± 2.7	8.7	7.2	6.8
30	6.1 ± 2.3	5.7 ± 3.6	7.8	8.6	5.5
31	11.1 ± 5.5	10.3 ± 6.7	10.1	7.6	6.3
32	12.6 ± 2.4	7.2 ± 1.2	8.4	7.9	7.4
33	10.8 ± 8.5	4.9 ± 4.1	8.8	6.4	6.2
34	12.2 ± 7.2	6.8 ± 4.5	9.3	7.9	7.3
35*	12.1 ± 3.8	9.3 ± 2.0	9.5	7.2	
$\bar{x}$ ± SD	11.8 ± 3.0	7.4 ± 1.8	10.3 ± 2.4	7.7 ± 1.2	7.6 ± 1.2

* CSII treatment discontinued after 9 months.

table A-II. Mean HbA_1% (± SD) during 1-5 years of CSII treatment.

patient no.	years of treatment 1	2	3	4	5
1	8.0 ± 0.8	7.3 ± 0.7	7.1 ± 0.6	8.1 ± 0.5	7.5 ± 0.4
2	8.0 ± 0.7	9.1 ± 0.8	8.1 ± 0.2	8.2 ± 0.5	8.0 ± 0.4
3	8.0 ± 1.4	7.3 ± 0.6	6.8 ± 0.5	7.1 ± 1.1	6.9 ± 0.1
4	7.5 ± 0.8	7.6 ± 0.6	6.8 ± 0.4	6.3 ± 0.9	6.9 ± 0.4
5	10.5 ± 1.3	8.7 ± 0.8	7.7 ± 0.3	7.7 ± 0.6	
6	8.4 ± 1.6	8.3 ± 0.8	7.6 ± 0.5	8.5 ± 0.5	7.6 ± 0.5
7	8.5 ± 1.3	7.6 ± 0.6	6.8 ± 0.5	7.2 ± 0.9	6.9 ± 0.3
8	9.3 ± 1.6	9.2 ± 0.9	7.3 ± 0.5	8.5 ± 1.0	
9	9.5 ± 1.4	9.4 ± 0.8	8.6 ± 0.2	7.9 ± 0.5	6.9 ± 0.8
10	8.5 ± 2.2	6.6 ± 0.6	6.3 ± 0.3	7.5 ± 1.2	6.7 ± 0.4
11	8.4 ± 0.9	7.0 ± 0.7	6.5 ± 0.4	6.7 ± 0.9	
12	8.7 ± 1.0	7.0 ± 0.4	6.1 ± 0.4	6.7 ± 1.3	
13	9.2 ± 0.6	7.4 ± 0.8	6.8 ± 0.2	7.7 ± 0.3	
14	9.1 ± 1.6	7.1 ± 0.5	8.5 ± 0.6		
15	7.4 ± 0.1	6.7 ± 0.7	7.0 ± 0.8		
16	7.4 ± 0.7	6.3 ± 0.4	8.1 ± 0.5		
17	7.3 ± 0.6	8.8 ± 0.5			
18	7.2 ± 0.7	8.7 ± 0.9			
19	7.7 ± 0.9	7.2 ± 0.5			
20	7.0 ± 0.7	7.6 ± 0.6			
21	7.5 ± 0.7	8.1 ± 0.6			
22	6.5 ± 0.4	6.2 ± 0.6			
23	8.5 ± 0.3	7.1 ± 0.5			
24	8.0 ± 1.3	6.1 ± 0.2			
$\bar{x}$ ± SD	8.2 ± 1.9	7.6 ± 1.0	7.3 ± 0.8	7.6 ± 0.7	7.2 ± 0.5

table A-III. Mean blood glucose (MBG) values (± SD) during 2-5 years of CSII treatment.

patient no.	MBG (mmol/l) during CSII treatment
1	6.0 ± 3.1
2	7.4 ± 4.7
3	6.4 ± 2.0
4	5.6 ± 2.8
5	8.2 ± 3.2
6	5.5 ± 2.8
7	5.6 ± 2.3
8	6.4 ± 3.3
9	7.6 ± 3.6
10	5.8 ± 2.9
11	5.8 ± 2.8
12	6.8 ± 3.3
13	8.2 ± 3.9
14	5.1 ± 2.0
15	7.2 ± 3.2
16	7.2 ± 3.7
17	6.1 ± 3.4
18	7.8 ± 3.4
19	8.2 ± 4.0
20	7.3 ± 4.2
21	8.4 ± 4.1
22	6.0 ± 3.0
23	6.1 ± 2.0
24	5.4 ± 2.0
$\bar{x} \pm SD$	6.7 ± 1.0

table A-IV. Mean blood glucose (MBG) values (± SD) and mean HbA_1% during pregnancy in CSII treated patients.

patient no.	MBG (mmol/l) during pregnancy	mean HbA_1% during pregnancy
1	6.4 ± 1.2	6.7
2	5.5 ± 0.6	6.2
3	4.4 ± 0.5	6.4
4	6.5 ± 2.7	6.6
5	6.6 ± 3.5	8.4
6	6.4 ± 3.4	6.6
7	6.0 ± 1.3	6.7
8	6.7 ± 1.3	6.6
9	4.8 ± 2.1	7.0
10*	5.3 ± 2.0	7.1
	5.2 ± 0.8	7.3
11	5.9 ± 1.0	7.2
12	6.5 ± 1.9	6.9
13	4.8 ± 2.5	6.2
14	8.8 ± 2.6	7.3
15	5.9 ± 1.2	7.0
16	6.8 ± 1.2	6.7
17*	6.4 ± 3.2	7.3
	8.3 ± 1.6	7.5
18	5.1 ± 1.1	6.6
19	6.5 ± 2.3	7.3
20	6.1 ± 1.3	6.6
21	7.5 ± 0.6	7.4
22	5.2 ± 1.2	6.5
23	4.5 ± 1.8	7.2
24	4.8 ± 2.0	6.0
25	6.4 ± 0.9	6.2
26	5.3 ± 0.8	6.7
27	5.1 ± 0.7	6.5
28	6.8 ± 1.2	7.6
29	6.8 ± 1.3	6.8
30	6.2 ± 2.3	6.4
31	4.6 ± 1.8	6.6
32	5.4 ± 2.3	6.7
33	6.4 ± 1.0	6.9
34	6.7 ± 1.5	6.1
35	5.8 ± 0.7	6.5
$\bar{x}$ ± SD	6.0 ± 1.0	6.8 ± 0.5

* patient with 2 pregnancies during the study

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