CONTINUOUS SUBCUTANEOUS INSULIN INFUSION IN NEWLY DIAGNOSED DIABETIC CHILDREN

continue subcutane insuline infusie
in
nieuwe insuline-afhankelijke diabetes patiënten
op de kinderleeftijd

Proefschrift

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Voor mijn moeder

Ter nagedachtenis
aan mijn vader

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CHAPTER 1

THE PUMP STUDY: MOTIVES AND PURPOSES

Were I to await perfection,
my book would never be finished
Tai T'ung (ca. 1300 BC)

INSULIN DEPENDENT DIABETES MELLITUS

In the first century AD Aretaeus of Cappadocia described diabetes as "a wonderful but not very frequent affection among men being a melting down of the flesh and limbs into urine ...., life is short, disgusting and painful, thirst unquenchable, death inevitable".

The recognition of this disease with its enormous thirst and massive production of honey sweet urine is very old. Nowadays diabetes is known as a heterogeneous disorder. Insufficient production of biologically active insulin is a common denominator in almost all forms of diabetes. Insulin deficiency results in a variety of metabolic abnormalities (hyperglycaemia, increased lipolysis, increased gluconeogenesis at the cost of amino acids). The NIH National Diabetes Data Group discerns 2 types of diabetes mellitus: insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) (National Diabetes Data Group 1979). IDDM frequently starts in childhood. The incidence in the Netherlands is estimated to be 11.0 subjects per 100.000 inhabitants per year in the age group below 20 years (Vaandrager 1984). Since NIDDM seldom occurs in childhood it will be left out of consideration in this study.

Insulin is produced by beta cells in the pancreatic islets of Langerhans. In due time after clinical onset there is hardly any beta cell activity evident. An absolute insulin deficiency ensues. As insulin plays a key role in maintaining normal metabolism, this implicates a life-long dependency on exogenous insulin administration. Since insulin is a peptide which can not be administered orally, administration of injections at least once daily is necessary. Ten to 15 years after the onset of the disease severe complications may develop (micro- and macroangiopathy) resulting in a shorter life expectancy and a reduced quality of life (Deckert 1978). It is evident that this chronic disease and its consequences also influence life, the psychological well-being and development of patients, especially those of child age.

The cause of this destructive process, which is specifically directed against the pancreatic beta cells, remains to be elucidated. Current thought is that a hereditary susceptibility in combination with an environmental agent can lead to the development of IDDM (Cahill 1981). Immunological disturbances - cellular as well as humoral - have also been found at the onset of the disease (Bottazzo 1981, Buschard 1980, Lernmark 1981, Maron 1983). Their precise role has not yet been clarified.

REMISSION PERIOD

A special feature of the course of the disease in most patients is a remission period (or so-called honeymoon phase), occurring shortly after the start of insulin substitution. This period is characterized by low or even no exogenous insulin requirement, but with good glycaemic control. It then seems - certainly to patients and parents - as if the fate of the diabetic child has changed towards cure. The beta cell function appears to recover. Unfortunately, this remission is not permanent. On the contrary, it usually lasts only some weeks or months in children. The end of the remission period is characterized by an increased need for exogenous insulin to maintain an as normal as possible metabolism. Once again the beta cell function deteriorates and in time no more beta cell activity can be detected. In the next chapter the term remission period will be explained (page 13-14). Criteria will be provided in order to prevent confusion, since this could be easily possible considering the literature.

It is not surprising that the remission period fascinates many clinicians and researchers working in the field of diabetes. The occurrence of this period suggests that recovery of the beta cell function can take place after the clinical onset of IDDM resulting in an almost normal metabolism. This phenomenon of temporary recovery creates the impression that progression of the disease may be stopped with the right therapeutic intervention. Intervention in an early period might change the course of the disease, preserve some of the residual beta cell activity and prevent or delay the development of major complications.

The main question is how to accomplish beta cell recovery therapeutically in diabetic children. More knowledge of the cause of the ongoing destructive process might offer the possibility to develop specific intervention therapies.

There has not yet been an explanation for the cause of a remission period. Several studies suggest the involvement of patient and disease related factors. Age and symptoms at onset (metabolic disregulation) are suggested to be associated with the remission phase (Knip 1982, Ludvigsson 1977). Among younger patients incidence and duration of the remission period seem reduced. A severe ketoacidosis at onset seems also negatively associated with occurrence of a remission period. The relationship between immunological disturbances and the remission also remains unexplained. Several immunological abnormalities before and after clinical onset have been demonstrated, such as islet cell antibodies, insulin antibodies as well as changes in T-lymphocyte subsets. Whether these factors influence the remission period remains to be clarified.

Preliminary attempts have been made to prolong the remission period through different immune suppression therapies (Elliot 1981, Ludvigsson 1983). Since the side effects of long-term immune suppression are substantial and the influence of the immune system and its disturbances are not yet clear, this kind of treatment seems as yet unjustified (Rossini 1980). Caution

should be exercised, especially with children.

Retrospective studies suggest a beneficial effect on the remission period of a rapid normalization of the metabolic disturbances at onset (Knip 1982, Ludvigsson 1979). A tight metabolic control from onset onwards seems to improve the beta cell function in the first period of the disease. One study describes a significantly increased incidence and duration of the remission in adult diabetics, treated shortly after onset for several days by an artificial beta cell. They achieved an excellent metabolic control (Mirouze 1978). An intensified injection therapy - consisting of three or more injections a day, combined with self-control (home blood glucose measurements), has shown to exert a positive influence on the beta cell function, even in patients with a longer duration of IDDM (Madsbad 1981). This has resulted in one of the main questions of this thesis: does near normoglycaemia, obtained in newly diagnosed diabetic children, result in a preservation of the residual beta cell function? Obtaining a good metabolic control in young children raises - however - other problems. Injections cause stress in most children, especially in toddlers. Augmenting the injection frequency to more than twice daily might increase the already heavy burden on diabetic children. The stress induced by increased injection frequency, in combination with expected deterioration of the injection sites, may actually work against an improvement in metabolic control.

As a result of the recent development in technology in the field of insulin delivery devices, reliable continuous subcutaneous insulin infusion pumps (CSII) have become available in a size usable in children. With these pumps near normoglycaemia and restoration of the metabolic state can be obtained in IDDM (Sherwin 1980, Tamborlane 1979). The combination of available devices to pursue near normoglycaemia in diabetic children and the possible benefit of this improved metabolic control on the remission period has led to the setting-up of this pump study.

PUMP STUDY

The purpose is to investigate whether CSII improves the metabolic control and influences the residual beta cell function in diabetic children when started immediately after the onset of IDDM. Although the excellent metabolic control in adult diabetics of recent onset results in a considerable prolongation of the remission phase, an equal effect using CSII for children is uncertain. Incidence and duration of the remission phase seem to be inversely correlated to the age.

To evaluate the effects of CSII on metabolic control and the residual beta cell function in a small group of newly diagnosed diabetic children, a prospective randomized design has been chosen. Thirty children, consecutively referred to the Sophia Childrens' Hospital, have been treated from diagnosis onwards with either CSII or a conventional injection therapy (CT) consisting of one or two injections a day. Since remission in children usually starts in the first month after the onset and ends within a year, the results in this thesis are given of all

children after one year. A follow-up of two years has been chosen in order to obtain - if an effect of CSII on the beta cell function is noted - further information on the duration of the effect.

The execution of a prospective randomized study with pumps in children requires a specialized setting as base. The organization of the Diabetes Clinic and its policy for the treatment of IDDM are described in chapter three.

CSII has never been used for newly diagnosed diabetic children. Hence, it is imperative to evaluate carefully the psychological impact of its use. The feasibility of CSII in a group of unselected newly diagnosed diabetic children is the first question that has been investigated by this study. Problems or manipulation with the pump at home, the frequency of phone calls to the hospital and home visits by the nurse practitioner, reactions from and acceptation (problems) by the diabetic child and its family all have to be taken into account. To evaluate the psychological effect of diabetes and the treatments thereof on the child and its family, children and parents involved in this study (CSII and CT!) have been submitted to a psychological test at the end.

The second question is whether CSII will lead to a better metabolic control. Metabolic control is evaluated by a regular determination of stable glycosylated hemoglobin. The insulin dose, home measured blood glucose levels, some intermediary metabolites and lipid metabolites are also included as parameters for metabolic control.

The influence of CSII on the incidence and duration of the remission period is the third question which is examined in this study. Assessment of the endogenous insulin secretion is one of the main parameters of the study. To determine the endogenous insulin secretion, C-peptide levels have been measured in plasma and urine. The logical consequence of the third question is the determination of factors by which the results can be explained. Several parameters have been determined for this purpose. As it has been suggested that metabolic control exerts a beneficial effect on the residual beta cell function, the relationship between stable glycosylated hemoglobin and the beta cell function will be evaluated. The contribution of the immune system to the remission period also remains to be elucidated. Several humoral factors, insulin antibodies and islet cell antibodies, have been measured. To evaluate the importance of genetic factors, discovered so far, and the possible influence of environmental agents, tissue typing has been performed and virusserology has been determined. The fourth chapter describes the exact design of the study, the statistical methods used along with these parameters.

The characteristics of the participating children and the results after one year of follow-up are given in chapter five.

The results are discussed in chapter six and since research never gives only answers, but always provides new questions, some suggestions are given for future research.

In summary, this prospective randomized investigation has been undertaken to study the effect of CSII on the metabolic control

and the remission period of newly diagnosed insulin dependent diabetic children. Since CSII has not been used before in a not selected group of children, the feasibility and psychological impact of the treatment are also evaluated.

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CHAPTER 2

THE REMISSION PERIOD IN INSULIN REQUIRING DIABETIC CHILDREN

INTRODUCTION

In the natural course of diabetes mellitus the acute onset is often followed by a clinical remission. The remission period or so-called honeymoon period is characterized by relatively low or no exogenous insulin requirements and good metabolic control. It suggests a functional recovery of beta cells. Many investigators are fascinated by this phenomenon, since it raises hope that a reversal, or at least intervention in the ongoing destructive process may be possible. Retrospective studies suggest that this period - its occurrence and duration - can be influenced by a tight metabolic control. In this thesis the remission period is studied and an attempt is made to evaluate its relationship with the metabolic control in diabetic children.

Before concentrating on the remission period, a short outline is given of current knowledge of IDDM, its etiology and natural course and of the psychological impact of this chronic disease on children. After defining the criteria for remission several aspects - morphological, metabolical and immunological - are discussed. Subsequently the possible benefit of the remission period and the attempts, undertaken so far to influence its course, are described. The chapter ends with a summary.

INSULIN DEPENDENT DIABETES MELLITUS

The course

One may divide the course of IDDM into three periods (figure 2.1). The first one (I) is the period with genetic susceptibility without beta cell mass destruction. The second period (II) starts after the triggering of the immune system by an environmental factor or by a spontaneous anti-self reactivity, resulting in destruction of beta cells. In this period islet cell antibodies (ICA) can appear, recognizing the islet cell (Lernmark 1981). The endogenous insulin production may be fluctuating but is still sufficient and above a certain critical level in order to maintain normoglycaemia.

The presence of an abnormal first phase insulin response to an intravenous glucose load has been demonstrated in this period (Srikanta 1983). The duration of the second period is unknown. ICA have been detected up to thirty months before the development of the overt disease (Gorsuch 1981). In some subjects however, these ICA disappear without any sequelae, suggesting that ICA detection does not always presage IDDM (Helmke 1980). At a given moment, the critical level of beta cell mass to guarantee normo-

glycaemia has been passed and clinically overt IDDM develops as the third period (III).

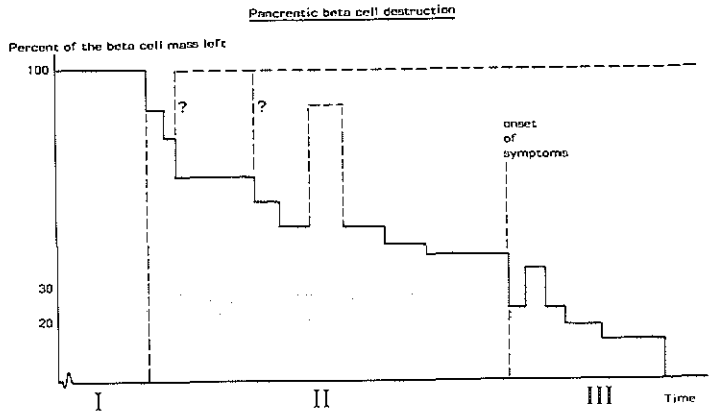

Figure 2.1. The time course of IDDM.
From dr G.J. Bruining, with kind permission

The appearance of the disease is highly variable. In some patients increasing polyuria and polydipsia may be present for several months before there is such a marked degree of weight loss and debilitation, that they are brougt to a physician's attention. In others the onset may be explosive with only a few days of subjective symptoms before ketoacidosis occurs. From this moment onwards insulin injections in combination with a diet are necessary for the rest of the patients' life.

One of the unique features of the natural history of IDDM is the remission period, central theme of this thesis. The majority of children will go through such a period. The duration of this period varies, but hardly ever lasts longer than one year. It will be outlined in the following paragraph.

For 10 to 15 years after the diagnosis of IDDM, chronic complications are uncommon. After that period, microangiopathy and macroangiopathy often develop resulting in severe complications such as retinopathy, nephropathy and neuropathy (Deckert 1978). Life expectancy is shortened and deterioration begins. The cause of these complications has not yet been elucidated. Indirect arguments from biochemical, enzymatic and functional studies show that optimal insulin and/or blood glucose control reverse some early diabetic changes that are probably related to the late events (Brownlee 1981). Several data suggest that the mechanisms responsible for diabetic microangiopathy are initiated as a result of insulin deficiency. The development of the microvascular complications of diabetes may be inhibited and/or delayed by careful control of blood glucose levels (Engerman 1977, Tchobroutsky 1980). However, the possible importance of ge-

netic susceptibility for microangiopathy as well as the influence of immunological disturbances on the development of the vascular complications can not yet be excluded (Andersen 1976, Mancini 1969, Schernthaner 1979).

With all the unanswered questions and with the prognosis in mind, it is not surprising that extensive research is done in the field of diabetes, its complications and the prevention of both.

Prevention in the first period and intervention in the second phase would both prevent the overt disease. Identification of the subjects at risk as well as more knowledge on what is going on is necessary before an effective prevention can be realized. When the disease has become clinically manifest - the third phase of IDDM - insulin therapy via injections and diet are prescribed to achieve an as normal as possible metabolism. This means the start of a life-long dependency on insulin.

The cause

Genetic susceptibility combined with an environmentally initiated - perhaps viral - perturbation of the immune system is suggested to result in the autoimmune destruction of the host's own beta cells (Cahill 1981, Craighead 1978).

Almost two decades ago the inheritance of IDDM was said to be a geneticist's nightmare. Rotter recently stated that the nightmare may gradually be subsiding but a headache still remains. A striking association has been found between the histocompatibility alleles (HLA-Dr 3 and Dr 4) and IDDM (Nerup 1978, Platz 1981). Thus inheritance may be related to one or more genes on chromosome 6 in association with the HLA complex. This association suggests an immunopathological process, occurring either as an isolated phenomenon or, more likely, as one initiated by a sensitizing insult to the beta cell. Hence, certain HLA factors may also be associated with the course of the disease. This emphasizes the importance of tissue typing of the patients participating in this study.

As initiating factors viruses and chemical factors have been mentioned. The hypothesis, that a viral infection may precede the onset of IDDM is supported by a case report, describing the development of a fatal insulin requiring diabetes in a previously healthy boy of 10 years of age after an influenza-like illness. Culture of pancreatic homogenates led to the isolation of Coxsackie B4. Inoculation of this virus into mice produced hyperglycaemia (Yoon 1979). Mumps, rubella and cytomegalyvirus have also been mentioned in association with the origin of some cases of IDDM (Ratzmann 1984). Chemical factors in the environment may also be diabetogenic (Helgason 1981, Karam 1980). Although initial factors are seldom found in newly diagnosed diabetics, the determination of virusserology has been included in this investigation.

The autoimmune reaction, either spontaneous or as a consequence of external factors, is demonstrated by the presence of the auto-antibodies, cell-mediated cytotoxicity or both. The possible

involvement of the immunologic disturbances at the onset of IDDM and in the first period thereafter is discussed elsewhere (page 16-17).

The psychological impact of IDDM in childhood

The onset, the course and the treatment of IDDM are particularly stressful for children. Which other disease requires daily self administration (or by parents) of medication with hypodermic syringes, with the threat of disaster if this practice is not observed? A chronic disease such as diabetes entails different challenges, tasks and responses at various moments in time, since it affects almost continuously the every-day life, not only of the child but also of its family. The diabetic children are frequently faced with their diet restriction (especially at secondary schools with their wide consumption of sweets and candy). It may not be surprising that this disease influences the psychological development of diabetic children. Psychological problems can, in turn, affect the metabolic control and thus the course of the disease (Anderson 1980, Hauser 1979, Simonds 1981). Thus far, conflicting results have been published, concerning the influence of IDDM on the psychological development (Hauser 1979, Sullivan 1978, Swift 1967). Sullivan suggests, that diabetes - in adolescent girls - emerges only as a focus for the expression of normal adolescent conflicts. Swift, on the contrary, finds significantly more psychopathology in diabetic children.

Intensification of the therapy and the diabetic control (with CSII or multiple injection therapy) results in a significant reduction of depression and anxiety and in a more positive "self-concept" in diabetic patients (Seigler 1982). With CSII mealtimes can be varied. For extra food the insulin dose can be easily adjusted. This may promote the participation of the child in activities of its peer group. It may also relieve some strain of the family. Considering the expected beneficial effect of CSII on the metabolic control, possibly reduced physical complaints may also promote the activities of the child. On the other hand the constant confrontation with the disease, carrying a visible device, can induce feelings of shame and a sense of inferiority. This may lead to withdrawal of the children from their peer group. Whether CSII in children has a positive effect is studied in this project.

For patients, especially children with IDDM, the role of the family is very important. Drash and Becker discuss several reasons why the family is so critically involved: (1) family members are constantly required to make clinical judgements that affect management decisions and (2) the diabetic regimen overlaps with, and usually restricts, many well established family routines (Drash 1978).

It is evident, that many factors, such as age, sex, interfamiliar interactions and others, are relevant for the psychologi-

cal impact of IDDM. An attempt is made to gather some information on the influence of CT and CSII therapy on the psychological well-being of diabetic children. Preliminary and not yet complete results are given in this thesis.

REMISSION PERIOD

Definition and parameters

In the 1940's Lieutenant Commander Brush described a period of functional recovery of the "islet apparatus" starting six to ten days after the onset of the disease and the start of the insulin treatment (Brush 1944). Starting in newly diagnosed diabetic children a treatment consisting of a strict diet and large amounts of insulin resulted after several days in a functional recovery of the islets and a considerable reduction in exogenous insulin (2 to 8 units). During subsequent weeks to months these children were essentially free of glucosuria. They seemed to achieve a steady state of endogenous insulin production.

Thus, shortly after the onset of IDDM a decrease in the exogenous insulin need can be observed, suggesting the recovery of beta cell function (Park 1974). It often creates a false hope of cure in children and their parents, for it raises the expectation that in due time no more insulin administration will be necessary. Unfortunately, nothing is less true. This remission period, usually starting in the first month after the start of the treatment, lasts several months at maximum and eventually ends with an increase in exogenous insulin need (Drash 1980). A considerable variation in frequency (25 to 100%) as well as in duration (1 month to 13 years) has been described (Ludvigsson 1980, Madsbad 1983). An exact definition of the remission period may contribute to a more consistent result.

First of all a clear difference must be made between total clinical remission and a partial clinical remission. A total clinical remission indicating normoglycaemia without any exogenous insulin administration is a very rare phenomenon in childhood diabetes (Pirart 1971). Only a few cases have been described (Weber 1972). The term partial clinical remission is usually used with respect to the period shortly after the clinical onset. This partial remission fits to the description given earlier: a clinical improvement coinciding with a reduction in exogenous insulin requirement. In this thesis the term remission period refers to a partial clinical remission.

Several criteria have been formulated for the remission period (Akerblom 1980). Some authors define it as a period, lasting for at least one month, in which insulin requirement is less than 0,5 U/kg per day and glucosuria is absent or minimal. Others do not include the insulin dose in the definitions as this depends to some extent on the policy of the responsible physician (Ludvigsson 1978). If this policy could clearly be explained however, the insulin dose would be a valuable parameter in the assessment

of the residual beta cell function. Glucosuria is often used to assess the overall metabolic state. It depends inter alia on the renal threshold of the child. Most authors do not mention when or how often glucosuria is determined: for example after an overnight fast? To get a correct impression of the metabolic control glucosuria ought to be measured in every urine voiding. Present possibilities of assessing the overall glycaemic control by way of stable glycosylated hemoglobin (sHbA1) may offer a more reliable parameter for the glycaemic control.

One of the most important features of the remission period is the apparent improvement in beta cell function. Hence a parameter to estimate the beta cell function has been included. C-peptide is secreted in the same quantity as insulin into the portal circulation but is, contrary to insulin, not extracted to any significant degree by the liver (Kühl 1978). The development of an assay for the determination of C-peptide has provided a valuable tool for direct studies of the endogenous insulin secretion in insulin dependent diabetic subjects (Block 1973).

Thus, following 3 criteria are taken into account in this thesis when considering the remission period: the insulin dose, the overall glycaemic control and the endogenous insulin secretion. A remission period is characterized by an insulin dose below 0,5 U/kg/24 hours, a sHbA1 and a C-peptide production within the normal range.

Morphological changes

Morphologically the pancreas of insulin dependent diabetic subjects is characterized by a reduction in number and size of the islets of Langerhans, as has been described by Gepts (Gepts 1981).

As long as beta cells can be determined, inflammatory changes such as insulitis can be observed in children up to about six months after the onset. In this period regeneration can also be found. Two types of islets seem to be formed after the onset of IDDM. The small new islets, proliferating out of the epithelial cells of the distal parts of the excretory ducts are composed of hyperactive beta cells with a high RNA and low insulin content. These islets are irregularly distributed throughout the pancreas. Especially after a longer duration more and more atypical islets, composed of sinusuoid cords of cylindrical cells and identified as PP cells, can be found. In time the regenerative capacity of the pancreatic tissue, which has probably already been strained before the clinical onset of the disease, deteriorates. This leads more and more to the development of the atypical PP cells.

Hence, in the first period after diagnosis regeneration and hyperactivity of the beta cells can be noted. Both disappear in time and sooner in younger patients. Since pancreas biopsies are still hazardous, it is not possible to distinguish what the contribution of these factors is to the remission period. The development of the C-peptide assay has provided a tool to assess the residual beta cell function. Although one can not distinguish hy-

peractivity and regeneration with this method, it offers valuable information on the functioning of the beta cells. It is evident that the determination of the C-peptide production is one of the main parameters of this study.

Whether this regeneration, the hyperactivity and the eventual degeneration reflect the natural course of diabetes is unknown. One may speculate that these phenomena occur as well before as after the overt onset of IDDM. Exceeding a critical level of remaining beta cell mass (necessary to maintain normoglycaemia) would result in that case in the clinical manifestation of diabetes. If so, the remission period may reveal further information on the pathogenesis of IDDM.

Metabolic abnormalities

The decreasing insulin levels lead after passing a critical level to hyperglycaemia, an increased lipolysis and ketogenesis (Cherrington 1982). Several products of these processes - such as non-esterified fatty acids (NEFA) - are known to reduce the effect of insulin on the peripheral tissues.

At the same time an increase in glucagon, catecholamines and cortisol levels can be observed. These hormones are also known as insulin antagonists. Their increased concentration will provoke in the absence of sufficient insulin levels a further increase of lipolysis and ketogenesis (Johnston 1982). Thus a circulus vitiosus is created, which will be interrupted by the start of insulin therapy. The reversal of this process and the decreased concentration of insulin antagonists may contribute to improved metabolic control. This increase in insulin sensitivity effect after the start of the treatment may be associated with the occurrence of a remission period. Since not all patients go through a remission period the phenomenon of remission does not seem fully explained by an increase in insulin sensitivity alone. Retrospective studies suggest that the seriousness of the metabolic disregulation at onset and the metabolic control after the onset show indeed an association with the occurrence and duration of the remission period (Knip 1982, Ludvigsson 1977a). Ludvigsson used serious ketoacidosis with drowsiness (not further specified), presence of ketonuria and blood glucose levels as parameters for the seriousness of metabolic disregulation at onset of diabetes. Knip includes as parameters for metabolic disregulation blood glucose levels, plasma ketostix ®, urine ketostix ®, blood pH (capillary) and blood carbon dioxide (capillary). In this thesis serious ketoacidosis, reflected in a blood pH below 7.2, the presence of ketonuria and blood glucose levels are used as parameters for metabolic disregulation at the clinical onset of IDDM. Overall glycaemic control after the onset of IDDM is reflected in glycosylated hemoglobin levels. Several intermediary metabolites have also been included in this study to evaluate the metabolic control of diabetic children.

Immunological disturbances

IDDM demonstrates a high incidence of antibodies directed against the pancreatic islet cells (Bottazzo 1981, Lernmark 1981). At diagnosis antibodies reacting with intracellular components of islet cells are often present (in 60-70% of the subjects). These islet cell cytoplasmic antibodies (ICCA) can be complement fixing, probably dependent on the titer of the ICCA (Bruining 1984). In a large prospective study ICCA have been demonstrated before the onset of IDDM, suggesting a possible role for them as marker for the ongoing beta cell destruction (Gorsuch 1981). Literature gives mixed results concerning the relationship between ICCA and residual beta cell function (Crossley 1981, Madsbad 1980, Mustonen 1984). However, the pathogenetic importance of ICCA seems less likely, since they solely react with intracellular components, which are inaccessible in living cells.

Islet cell surface antibodies (ICSA), on the other hand, bind to component(s) facing the exterior of the cells (Van de Winkel 1982). Their capability to mediate a complement-dependent cytotoxic reaction may eventually lead to membrane lesion and cell death, thus suggesting a possible involvement in the pathogenesis of IDDM. In vitro studies suggest that ICSA alters the insulin secretion of beta cells (Kanatsuna 1982). Whereas Kanatsuna describes an inhibitory effect of these ICSA on the beta cell function, Nielsen finds that sera of newly diagnosed diabetic patients stimulate the insulin production of mouse islets (Nielsen 1981). Thus, ICCA and ICSA may play an important role in IDDM, either as marker for beta cell destruction or as factors involved in the destructive process.

Not only against the hormone producing cells but also against the hormone itself antibodies can be detected. Injected insulin is immunogenic and the administration of even human insulin may induce an antibody production. Conflicting data have been published on the relationship of these antibodies with the metabolic control or with the remission period of patients (Asplin 1978, Ludvigsson 1976, Ludvigsson 1977b). A recent study describes the presence of autoantibodies against insulin before the start of insulin injections (Palmer 1983). This indicates that these antibodies may also be involved in the pathogenesis of IDDM.

Maron and co-workers demonstrate the presence of antibodies in sera of newly diagnosed diabetic children exerting an insulin-like effect on fat cells (Maron 1983).

The complexity of the immunological disturbances is evident. It can certainly not be excluded that other - not yet identified - antibodies play a role in the pathogenesis of IDDM. The antibodies may influence the beta cell function or cause their destruction. They may be produced only after the start of the destructive process as epiphenomenon or as marker of beta cell destruction. Antibodies may influence the effect of insulin, positively or negatively, at the level of the receptor.

Not yet mentioned is the cellular immunity. At diagnosis of IDDM a reduced suppressor T-cell concentration is found in the

presence of an increased quantity of killer T-cells (Buschard 1980, Pozzilli 1979). In this thesis several antibodies have been determined in order to obtain further information on the humoral disturbances present in IDDM and possibly influencing its course.

Possible benefit of the remission period

Possible benefit of any residual beta cell function for the long term has been shown by a Danish group (Deckert 1980). They have found significantly less eye complications in patients with longer than 15 years IDDM who had some residual beta cell function compared with those having no beta cell function left. It is tempting to suggest that some residual beta cell function might contribute to a delay or even to prevention of the late diabetic complications. The results of Deckert have not been confirmed by others (Bodansky 1981).

Another merit of the residual beta cell function has been shown by insulin withdrawal studies (Madsbad 1979). Deprivation of insulin results in later occurrence of hyperglycaemia and ketonbodies in patients who had some residual beta cell function compared with patients without any residual beta cell function. This suggests a decreased risk for a fast metabolic disregulation, so often resulting in hospital admittance because of severe ketoacidosis. During the first ten hours of insulin withdrawal patients without any beta cell function decompensate faster despite similar peripheral free insulin concentrations. In healthy subjects about 50 to 70% of the secreted insulin is extracted immediately by the liver, without having circulated in the peripheral tissue. Exogenously administered insulin first "travels" through the periphery towards the heart to arrive finally in the liver. To get a similar effect on the liver more insulin is needed. The relatively large amount of insulin administered peripherally might reduce the sensitivity of the peripheral tissue, whereas centrally (in the liver) still an insufficient effect of insulin can be observed. This emphasizes the importance of some residual beta cell function.

It is evident that further metabolic importance of even a minimal degree of preserved beta cell function might be based on the finding that the beta cells are capable of modulating insulin secretion in response to variations in blood glucose concentration (Madsbad 1982). Although the first phase response of the beta cells may have disappeared, the tops of the swings in blood glucose concentrations may be reduced by the endogenous insulin production, contributing to an improved metabolic control (Madsbad 1983).

Finally the remission period may reflect the natural course of IDDM, thus offering the opportunity to obtain more information on the pathogenesis of the disease. It also raises the expectation that with an adequate therapy further progression of the disease may be stopped. A prolongation of the remission period (if possible unlimited) will improve the life expectancy and the quality of life of the diabetic patients (Madsbad 1982).

Attempts to influence the remission period

Especially for insulin dependent children the impact of the diabetogenic process is usually greater during the first 12 months after diagnosis (Crossley 1981). Potential therapeutic efforts to limit islet cell damage need to be applied early. It is possible that these efforts may not need to be continued much beyond 12 months after diagnosis.

What has been done so far to preserve residual beta cells and to prolong the remission period?

Two main approaches can be distinguished in attempts to influence the occurrence of a remission period and the preservation of the residual beta cells by therapeutic means.

One approach originates from the hypothesis that insulin-requiring diabetes may be an autoimmune disease, smoldering for many years before becoming clinically apparent. Immunosuppression or, even better and more specific, immunomodulation may prevent further damage of beta cells. Glucocorticoids, human leukocyte interferon, levamisole, plasmapheresis, cyclosporin A, and antilymfocyte globulin all have been tried (Elliot 1981, Ludvigsson 1983, Rand 1981). There have been no reports of total cure (completely normal oral glucose tolerance and return of the first phase insulin release after intravenous glucose), although euglycaemia of variable duration with a normal sHbA1 is possible. An obvious consideration is that dosages, timing and duration may not have been ideal. Before considering other more extensive, prolonged and aggressive immunotherapies, it might be useful to emphasize looking not only at possible benefits but also at risks of immunotherapy, especially in children. Of course, not all immunotherapy is the same in terms of toxicity and potential efficacy. The risks are not trivial and are related to the intensity and duration of therapy. The possible benefit is the cure of diabetes. At present this has still not been achieved by immunoregulatory therapy after the clinical onset of the disease.

The other approach towards preservation of the residual beta cell function derives from retrospective studies, which suggest a possible benefit of a good metabolic control immediately after the clinical onset (Gillet 1980, Knip 1982, Ludvigsson 1977a).

Those patients, having received a more vigorous treatment in the first days after clinically overt onset, have both a higher incidence of remission and a better metabolic control.

One prospective study describes a significantly higher incidence of remissions in recent onset diabetics treating them for a short period with an artificial pancreas thus achieving an excellent metabolic control (Mirouze 1978).

The achievement of normoglycaemia has been a very difficult task for a long period, especially in children. Frequent injections are known to result in a good metabolic control. However, an increase in injection frequency in children does not always result in better control. An increase of stress factors as well as deterioration of injection sites (indicating a less predictable resorption and effect of insulin) may be the result. Self monitoring, the possibility to measure and adjust blood

glucose levels at home, forms a great improvement in the therapy of children. But more is necessary to obtain near normoglycaemia, for there is a limit to control of blood glucose levels via finger pricks and adjustment by extra insulin injection.

Recent technological development offers new possibilities (Pickup 1980, Soeldner 1981). The insulin delivery devices produced nowadays have a size applicable in children. With these devices a restoration of the metabolism can be obtained (Pietri 1982, Sherwin 1980, Tamborlane 1979). Continuous administration of insulin with the boluses for each meal is a better imitation of the physiological situation than injections once or twice daily (page 27). These devices may be useful in achieving a tight metabolic control in the newly diagnosed diabetic child without limiting the child in his movements. Until now CSII has never been used in a randomized group of newly diagnosed diabetic children.

The pump study, as described in this thesis, has been undertaken to evaluate the benefit of a strict metabolic control - obtained by CSII - on the remission period in newly diagnosed diabetic children.

SUMMARY

1. In the natural course of IDDM three periods can be discerned:
   I. only genetic susceptibility
   II. beta cell destruction without any clinical symptoms
   III. clinically overt diabetes with its sinister prognosis.
   A genetic susceptibility combined with an environmental agent may cause an immunological perturbation that leads to the autoimmune destruction of the beta cell mass. This will result in insulin requiring diabetes mellitus.

2. The remission period, frequently occurring shortly after clinical onset of IDDM, is characterized by a relatively low or no insulin need with good metabolic control. In this study the combination of following 3 criteria is used for a remission period: an insulin dose below 0,5 U/kg per day, a sHbA1 and C-peptide production within the normal range.

3. The psychological impact of IDDM in children depends upon many factors. The influence of 2 different therapies (CSII and CT) on the psychological well-being of diabetic children is studied and preliminary results are given in this thesis.

4. Morphologically the remission period is characterized by regeneration and hyperactivity of the beta cell mass. Metabolic abnormalities present at the onset of IDDM are reversed by insulin therapy. This may lead to an improved insulin sensitivity. Finally a variety of immunological abnormalities, cellular as well as humoral, against the organ as well as against its product can be observed. In this thesis an attempt is made to evaluate the relationship between these factors and the remission period in diabetic children.

5. A possible benefit of the remission period is the effect it may exert on the metabolic regulation. The association found between the decreased incidence of major complications and an endogenous insulin reserve is of great importance. This period may also offer opportunity for intervention in the ongoing destructive process after the clinical onset of the disease.

6. Attempts at intervention with immunosuppressive agents have not been too hopeful. A tight metabolic control may have a beneficial effect on the residual beta cell function. With the recently developed continuous insulin delivery systems achievement of tight control proves possible providing thus the opportunity to test the suggested benefit of a tight metabolic control on the occurrence and duration of the remission period.

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CHAPTER 3

THE TREATMENT OF INSULIN DEPENDENT DIABETIC CHILDREN: ORGANIZATION AND POLICY

INTRODUCTION

The aim of treatment of insulin dependent diabetic children is to achieve (near) normoglycaemia without hypo- or hyperglycaemic symptoms and with normal development of the child, physically and psychologically.

Until recently this aim has been pursued in the Sophia Childrens' Hospital, SKZ (part of the University Hospital Rotterdam); with the conventional injection therapy, focussing on self-control and home care. Recent technological development has introduced new possibilities: the continuous subcutaneous insulin delivery devices. This has led to the study described in this thesis. Without the present setting, the Diabetes Clinic in the SKZ, this study would not have been possible. In the first paragraph of this chapter some general remarks are made on the organization of the Diabetes Clinic, on the home care and the self-control, pertaining to CT patients. With pump therapy only little experience has been obtained before the start of this study. Regarding the home care and self-control of the pump patients the same applies. In the second paragraph the theoretical background of pump therapy is briefly explained. The chapter ends with a summary.

CONVENTIONAL TREATMENT OF DIABETIC CHILDREN

At the Diabetes Clinic of the Sophia Childrens' Hospital a diabetes team, consisting of two pediatricians (one pediatric endocrinologist, one general pediatrician), a nurse practitioner, a dietician and a research fellow during this study, is responsible for the care of about 150 diabetic children. Once a month a pediatric psychiatrist is consulted by this team to discuss problematic children. The pediatric endocrinologist - head of the team - and the research fellow work full time in the field of diabetes. The general pediatrician works (officially) for 20% on diabetes. The nurse practitioner devotes 70% of her time to the diabetic children.

Patient (and parent) education and self monitoring - at home - are the pillars on which the treatment of the children and their parents is based (Baum 1981, Bruining 1984, De Visser 1977). Hospitalization is reduced as much as possible. Whether hospitalization can be avoided at the onset of the disease depends on several factors: physical condition of the child (dehydration, ketoacidosis with a pH < 7.2), social background (telephone at home, knowledge of Dutch) and availability of the nurse practitioner.

Usually an intensive training is started at home during the first weeks (1-3) after the onset of the disease. The nurse practitioner is responsible for the training at home. The trai-

ning consists of practical skills as well as an explanation of the theoretical background. Several practical skills must be acquired in the first period after the onset of IDDM. The correct injection technique (administering insulin in the deep subcutaneous tissue) and methods to control the blood glucose level, ketonuria and glucosuria, are taught.

Usually the child will start with one insulin injection per day. On the basis of metabolic control (sHbA1 and home measured blood glucoses) this frequency may be increased to two injections a day. This change usually occurs after 6 to 12 months, commonly during an infectious disease. The thigh, the buttocks and the abdomen are the sites used for injections. In the beginning, often only the thigh is used, whereas in the following two years the other injection sites are included. Thigh and buttocks are considered to be similar with respect to the resorption of insulin. The abdomen as injection site, however, is suggested to result in a faster resorption of the administered insulin and is therefore not interchangeable with thigh and buttocks without precaution.

Blood glucose measurements are performed with 20/800 hemoglucotest strips (Boehringer, Mannheim, FRG). Glucosuria and ketonuria are measured with Ketodiabur test strips, or Ketur and Diabur test strips (Boehringer, Mannheim, FRG). In the first week after the onset of IDDM blood glucose measurements are performed once or twice daily (before the administration of insulin). When the child (and/or the parents) know how to perform the measurements they are requested to measure the blood glucose levels at different hours during the day, usually before and after the meals, at 00.00 hours and at 03.00 hours. Thus information is obtained on the glycaemic control at different moments.

After the initial period (after 3 weeks after the onset of IDDM) the patient and/or parents are advised to measure the blood glucose value about 3 to 5 times a week at different hours of the day and night. Achievement of blood glucose levels between 4.4 and 10.0 mmol/l is pursued. In special situations (some of them are listed in table 3.I) the frequency has to be increased in order to adjust the insulin dose adequately.

Table 3.I Special situations, requiring extra blood glucose measurements

- Intercurrent illnesses
- Parties
- Dinners
- Sporting activities
- Travelling

The determination of glucosuria as a parameter for glycaemic control in most cases has been replaced by blood glucose measurement. In very young children it is used in order to reduce the frequency of blood pricks. Ketonuria is measured when hyperglycaemia is found. It will give some information on the duration of hyperglycaemia (hyperglycaemia with ketonuria suggests a longer duration) and its presence indicates that more insulin is needed to reduce the blood glucose level towards normal.

The theoretical part of the training consists of information on the disease itself, the cause, the immediate therapeutic and dietary implications and the acute complications (hypo- and hyperglycaemia). The way insulin acts and the relationship between insulin, physical activities and diet are discussed. The different types of insulin are mentioned. Naturally time is taken to answer the parents and/or child's questions. Some time after the onset chronic complications, heredity and future possibilities are discussed.

During visits to the outpatient clinic the diet is discussed with the dietician. Taking into account as much as possible the nutritional habits of the family, a wholesome diabetic diet is composed. This consists of 15 à 20% protein, 30 à 35% fat (up to 15% of the fat unsaturated) and 50 à 55% carbohydrates. Since 1984 "fast" carbohydrates (such as glucose and fructose) can be included in the diet, provided that (a) they are taken in combination with a main course and (b) the quantity does not exceed 5% of the total caloric intake of that meal.

The aim of the training is to teach parents and children to control blood glucose values, ketonuria and/or glucosuria, to interpret these values in the context of a given situation and to consequently adjust diet or insulin dose adequately.
Certainly in the first year(s), the parents are advised to consult one of the members of the diabetes team in case the measured blood glucose levels exceed the limits or when ketonuria is detected.

A 24 hours telephone service provides the possibility to reach one of the team members at any time. Early adjustments of insulin doses or diet can thus be made in order to prevent longer or more serious metabolic disregulations. To avoid a long-continued hypoglycaemia every patient is provided with a glucagon infusion set (NOVO, Bagsvaerd, Denmark). This set consists of a syringe with i.m. needle, 1 mg glucagon and solvent. The parents are taught how (deep intramuscularly) and (hypoglycaemia with unconsciousness) glucagon must be used.

During the first month after onset the patient visits the outpatient clinic 2 to 4 times. Thereafter the frequency is reduced to a visit once every 6 weeks or 3 months, dependent on the degree of metabolic control. During these visits several members of the diabetes team see the patient: the doctor each visit and usually the nurse practitioner and the dietician. During each visit weight and length are measured to obtain information on the development. After each visit the patient's problems, general condition and the laboratory results (sHbA1) are discussed by the diabetes team. If necessary, proposals are made to change the

insulin dose and/or diet. The nurse practitioner informs the patient (or its parents) by telephone of the laboratory results and the proposals made. Sometimes, circumstances or specific problems necessitate an extra home visit by the nurse practitioner. Problems can be of any nature, purely practical, psychological, questions regarding school, etc.. Before a holiday abroad a short refresher course is sometimes given. If required, instruction is given by the nurse practitioner to schoolteachers, trainers etc..

About one-half to one year after the onset of the disease the parents are invited to participate in a refresher course lasting 5 evenings (20.00 - 22.00 h.). This course consists of a recapitulation of the theoretical aspects of diabetes, the treatment and adjustments of insulin dose or diet in special situations. Parents' questions as well as recent developments in the field of diabetes are discussed. These evenings offer not only the opportunity to repeat the first training but they create the possibility to talk about and discuss common experiences with other parents. Usually about 70% of the parents attend these evenings.

In general patients leave the pediatric hospital to attend the outpatient clinic for adults (Dijkzigt Hospital, part of the University Hospital Rotterdam) at the age of 18 years.

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION PUMP TREATMENT

The use of continuous subcutaneous insulin infusion devices is expected to result in a more physiological administration of insulin, hence a better metabolic control.

Although CSII still delivers insulin in the wrong place - in the peripheral subcutaneous tissue - the administration of a basal rate, combined with boluses before each meal, results in a better imitation of the physiological situation. In simple terms, the beta cell delivers insulin into the blood stream at two rates: a continuous slow basal rate, which controls glucose output from the liver and restrains lipolysis and proteolysis, and mealtime bursts which dispose of the digested nutrients. Diurnal profiles of free insulin in CSII patients, CT patients and the range for healthy volunteers are shown in figure 3.1 (Home 1982). These profiles have been made in adults. They indicate that the free insulin levels in CSII patients approximate the normal range. The curves of the CT group differ considerably however, especially between the meals.

The indications for CSII treatment in children are examined by this study. Only one diabetic child in the SKZ already begun with CSII before this study because of a brittle diabetes, characterized by frequent and serious ketoacidoses requiring hospitalization (Natham 1982).

Because of ignorance about problems related to this treatment in children, the costs of pump treatment (Appendix II), the risks of it (Teutsch 1984) and no guarantee for an optimal metabolic control (Bruining 1983) indications for starting such a treatment have to be carefully formulated.

STELLINGEN

1 Continue subcutane insuline infusie pomp therapie bij nieuwe niet geselecteerde diabetes patiënten op de kinderleeftijd is goed uitvoerbaar, mits de opvang door het behandelend team aan bepaalde eisen voldoet.
(Dit proefschrift)

2 Kinderen, die vanaf het moment dat bij hen insuline afhankelijke diabetes mellitus is vastgesteld, behandeld worden met continue subcutane insuline infusie pomp therapie, vertonen in het eerste jaar een betere metabole regulatie (wat betreft het geglycosyleerde hemoglobine) dan kinderen, die conventioneel behandeld worden.
(Dit proefschrift)

3 Indien bij kinderen van vijf jaar of jonger insuline afhankelijke diabetes mellitus wordt geconstateerd, verdient het aanbeveling deze patiënten vanaf het begin met pomp therapie te behandelen.
(Dit proefschrift)

4 De correlatie tussen de endogene insuline productie van insuline afhankelijke diabetes patiënten bij de diagnose en na één jaar geeft weer, dat gestreefd moet worden naar een zo vroeg mogelijke ontdekking en behandeling van deze aandoening.
(Dit proefschrift)

5 De aanwezigheid van insuline antistoffen vòòr het starten van insuline substitutie bij insuline afhankelijke diabetes patiënten is geassocieërd met een snellere afname en een geringere produktie van endogene insuline. Dit suggereert, dat deze antistoffen een 'marker' zijn voor beta cel destructie.
(Dit proefschrift)

6 Gelet op de gevoeligheid van de thermo-esthesiometer en de geringe belasting van deze meetmethode voor de patiënt, lijkt deze techniek een veelbelovende parameter voor de vroegtijdige ontdekking van stoornissen in de perifere zenuwen van kinderen met insuline afhankelijke diabetes mellitus.
(Bertelsmann F, J of Neurol, Neurosurg and Psychiatry 1985, blz 686 - 690)

7 De ethische eis, dat aan niet-therapeutische ingrepen bij kinderen slechts minimale risico's verbonden mogen zijn, is niet voldoende genuanceerd. Het is de vraag of deze restrictie onverminderd geldt in het geval van niet-therapeutische ingrepen bij gezonde zusjes of broertjes van zieke kinderen, indien eerstgenoemden zelf bereid zijn meer dan minimale risico's te aanvaarden.
(Contra : De Beaufort I D, Ethiek en medische experimenten met mensen 1985, Van Gorcum, Assen)

8 De gedachte, dat het in termen van racisme interpreteren van kinderboeken als BABAR en LITTLE BLACK SAMBO de jongere generatie voor dit kwaad kan behoeden, is evenals vele andere ontsproten aan een wens.
(Contra : Dixon B, Catching Them Young; Sex, Race and Class in Childrens' Fiction 1977, Pluto Press, Londen)

9 Vrouwen, die om financiële redenen draagmoeder willen worden, dienen zich af te vragen of het kind niet het kind van de rekening zal zijn.

10 De aanbeveling* om de interpretatie van het Verdrag betreffende de Status van Vluchtelingen (Genève 1951) zodanig te verruimen, dat diegenen, wier mensenrechten op grond van sekse worden geschonden, kunnen worden begrepen onder 'bepaalde sociale groep' (zoals genoemd in artikel I van de Conventie van Genève betreffende de Status van Vluchtelingen 1951), dient zeker ook door vrouwelijke artsen te worden ondersteund.
*(Seminar 'Vrouwelijke Vluchtelingen' 1985, Soesterberg)

11 Het argument van H Nord (Vice-President van het Europese Parlement) tegen het beperken van het aantal werktalen in de instellingen van de Europese Gemeenschap luidt: Van de vertegenwoordigers van de lidstaten met een klein taalgebied mag niet de beheersing van een vreemde taal verlangd worden, alvorens zij kandidaat voor een functie of zetel kunnen zijn. Dit argument dient als remmend en onzinnig voor de Europese integratie beschouwd te worden.
(Contra : Nord H, Europa van Morgen, 15 januari 1986)

12 De woorden van François Robichon de la Guérinière " Niet een martelende onderwerping, maar buigzaamheid en ontspannenheid zijn de eerste vereisten voor (dan vrijwillig aangeboden) gehoorzaamheid van het paard" verdienen meer aandacht van de huidige ruiter.
(Een koninkrijk voor een paard, Isenbart H H, Bührer E M, Van Gaade, Den Haag)

13 Gelet op de publicaties en congresverslagen, waarin succesvolle isolatie technieken van humane eilandjes van Langerhans worden beschreven, is het verbazingwekkend, dat niet op grote schaal onderzoek gedaan wordt met in kweek gebrachte humane eilandjes.

14 Het verdient aanbeveling om de wetenschappelijke voordrachten tijdens wetenschappelijke congressen naar de pauzes te verplaatsen, omdat men mag aannemen, dat de informatie uitwisseling in de wandelgangen door de daaraan verbonden ambiance en het informele karakter effectiever is.

Carine de Beaufort,
1986

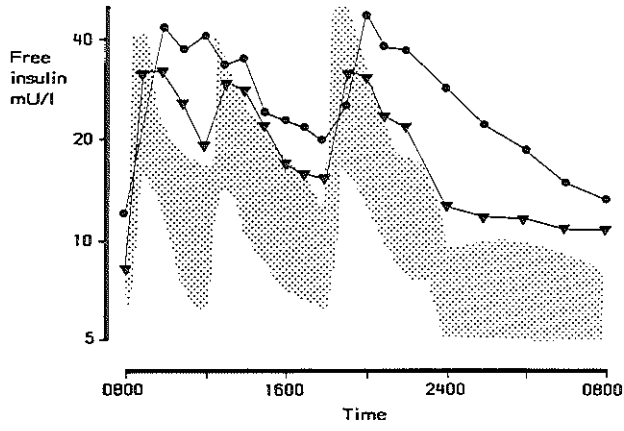

Figure 3.1 Plasma free insulin profiles in C-peptide negative diabetics (n = 10) on twice daily insulin injections (● - ●) and during continuous subcutaneous insulin infusion (▲ - ▲). The shaded area indicates the normal range for a group of healthy controls. Data from dr P. Home et al. with kind permission

SUMMARY

1. The aim of the treatment of insulin dependent diabetic children is to achieve (near) normoglycaemia, without hypo- or hyperclycaemic sypmtoms, and with a normal development, physically as well as psychologically.

2. Patient (and parent) education and self monitoring are supporting pillars for the treatment of insulin dependent diabetic children.

3. Hospitalization is reduced as much as possible. Theoretical and practical instruction is given at home by the nurse practitioner.

4. A frequency of 3 to 5 blood glucose measurements per week is recommended for all patients, whether treated conventionally or with CSII.

5. CSII is expected to result in a more physiological administration of insulin. The indications for CSII use in children can only be formulated when more experience has been acquired.

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CHAPTER 4

THE PUMP STUDY: COMPARATIVE RANDOMIZED STUDY OF CSII AND CT: DESIGN AND PARAMETERS

INTRODUCTION

The aim of the pump study is to evaluate the influence of CSII, started in not selected newly diagnosed diabetic children, on the remission phase in these children, compared with CT. This has resulted in the following questions:

- Is CSII feasible in not selected newly diagnosed diabetic children? What is the psychological impact of the therapy?
- What is the influence of CSII on the metabolic control?
- Does CSII prolong the remission phase in diabetic children?
- Which factors contribute to the remission phase? Which factors do not exert a (direct) influence on it?

The general design of the study, the parameters and the methods of determination are described in detail in the following paragraphs. The chapter will end stating in more detail the questions that are discussed in this thesis.

PUMP STUDY: DESIGN AND PROTOCOL

Design

To evaluate the effect of CSII treatment on the remission phase 30 children - consecutively referred to the Sophia Childrens' Hospital - are treated with either CSII or CT, consisting of 1 to 2 injections per day. In both groups semisynthetic human insulins (NOVO®) are used. Which child will receive which therapy is randomized, based on order of entry using a table of random permutations. The study has a final follow-up of 2 years. In this thesis an evaluation of the results after 1 year follow-up is given. This point of time has been chosen because several studies as well as experience in our clinic indicate that the mean duration of the remission period is less than one year (Knip 1982, Ludvigsson 1977). A final follow-up of two years has been chosen in order to obtain information concerning the duration of the possible effect.

Protocol

At the onset of IDDM several determinations have to be performed in order to confirm the diagnosis, to evaluate any direct trigger for the acute disregulation, and to assess whether hospitalization is necessary. These parameters are shown in table 4.I, group Ia and b. They are arranged in four groups:

(1) the initial parameters - usually determined at the onset of the disease - include inter alia HLA typing and virusserology,
(2) the parameters for metabolic control, consisting of stable glycosylated hemoglobin, home measured blood glucose levels, intermediary metabolites, cholesterol and HDL cholesterol,
(3) the C-peptide concentration as parameter for the endogenous insulin production, determined in 24 hours urine as well as in plasma,
(4) the immunological parameters, possibly involved in the aetiology and the course of IDDM, to wit ICCA, ICCA-CF, ICSA, IgGIa and IgGIb (page 132: list of abbreviations).

It has been suggested as previously mentioned, that the severity of metabolic disregulation influences residual beta cell activity (Ludvigsson 1977). In the result section only data relevant to the investigation are given, to wit blood glucose concentration, blood pH and ketonuria. The duration of symptoms before clinical onset and the duration of the hospitalization (if any) are also noted. Blood glucose concentration is determined by a glucose oxidase method (GOD-PAP, Boehringer, Mannheim, FRG). Blood pH is measured by a blood gas analyzer (ISL 1302, IJsselstein, Holland). Ketonuria is determined by test strips (Ketur strips ® or Keto-diabur strips ® Boehringer, Mannheim, FRG).

HLA typing (A, B, C and Dr) has been performed by the standard microcytotoxicity assay using peripheral blood lymphocytes. The typing has been performed by the Department of Immunohaematology and Blood Bank, University Hospital Leiden, Leiden (Head of Dept.: Prof. dr J.J. van Rood) (Van Rood 1979, Van Leeuwen 1980). All patients have been typed.

Virusserology has been performed to obtain, if possible, information concerning the direct trigger of the acute metabolic disregulation. The determinations for the detection of influenza A and B, adenovirus, RS virus, mycoplasma, parainfluenza 1, 2 and 3, psittacosis, mumpsvirus, german measles, measles and chicken pox virus, cytomegalyvirus, Ebstein Barrvirus, Q-fever virus, hepatitis B virus and herpes virus have been performed by the Department of Virology, Erasmus University and University Hospital Rotterdam (Head of Dept.: Prof. dr N. Masurel). Virusserology is considered positive if at least a 4 fold antibody rise in complement fixation is found or a specific IgM in a single sample is determined.

After confirmation of the diagnosis IDDM, the project and its purpose are presented to the child and its parents. The advantages and disadvantages of the 2 therapies are described as clearly as possible as well as the extra burden, arising from the par-

Table 4.I Protocol for laboratory tests

Time (weeks after the clinical onset)	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Parameters														
1.a. Blood: glucose, Na+, K+, Astrup, Hb, Ht, Leucocytes differentiation, bloodgroup, Urine: pH, glucose, ketones, albumin, sediment	o													
HLA typing	o													
b. Virusserology	o		o		o									
2. sHbA1	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Lactate							o							
Pyruvate							o							
3-OH-butyrate							o							
Triglycerides							o							
NEFA							o							
Amino Acids							o							
Cholesterol	o		o		o		o		o		o		o	
HDL-Cholesterol	o		o		o		o		o		o		o	
3. Glucagon Stimulation Test							o							o
Urinary C-peptide	o	o	o	o	o	o	o	o	o	o	o	o	o	o
4. Islet Cell Cytoplasmic Antibodies (ICCA)	o						o							
Islet Cell Cytoplasmic Antibodies Complement Fixing (ICCA-CF)	o						o							
Islet Cell Surface Antibodies (ICSA)	o						o							
Insulin Antibodies:														
(1) IgGIa	o			o			o			o			o	
(2) IgGIb	o													

ticipation in the study. If a positive decision is taken regarding participation in the study, therapy is started. In due time the parents receive a letter which outlines the study. Parents and children (12 years of age and older) are requested to sign in order to indicate their knowledge about and approval of participation in the study (Appendix I).

Pump treatment is started in the hospital. The children are hospitalized for about 10 days. During these first days the frequency of blood glucose control varies between 6 and 9 times in 24 hours (before and after each meal, at 0.00 hours and at 03.00 hours). After discharge from the hospital, this frequency is reduced to 3 to 5 times per week, except in special situations (page 26). The children, starting with the conventional treatment can usually leave the hospital after the administration of their (first) insulin injection. In general a combination of long (zinc or isophane) and short-acting insulin is injected. For more details on the conventional therapy the reader is referred to the third chapter (page 25 - 28).

During the first month, both groups of patients visit the hospital once a week. They are seen by the same doctor (the research fellow). The second month this frequency is reduced to once every other week.

From the third month onwards the patient visits the hospital once per month. At the hospital the patient is seen each time by the doctor and usually by the nurse practitioner and the dietician. After the initial period home visits are only made when necessary.

The parameters to evaluate the feasibility and psychological impact of CSII in children, include the frequency of home visits, the acceptation of CSII, problems with the pump, and psychological tests. The psychological tests are performed after two years of follow-up, resulting in a limited number of patients tested as yet and described in this thesis. The socioeconomic class has been assessed according to the occupation of the fathers (table 4.II).

At the end of the pump study, those patients who are treated by CSII are asked whether they want to continue the treatment. If their reaction is positive, a request for financial support for the continuation of the treatment is sent to their insurance company.

After the follow-up of two years the patients, conventionally or pump treated, enroll in the routine Diabetes Clinic program.

Table 4.II Classification of occupational levels

Socioeconomic classes	Occupation of the fathers
LOW :	1. Unskilled employees 2. Skilled manual employees 3. Clericals, technicians, minor professionals
MIDDLE :	4. Owners of small businesses 5. Supervisory, lesser professionals
UPPER :	6. Executives, major professionals Owners of large businesses.

ETHICAL CONSIDERATIONS

Before a study is begun in the Sophia Childrens' Hospital the study protocol has to be submitted to and approved of by the Medical Ethical Committee of the Medical Faculty, Erasmus University and University Hospital Rotterdam. No study can be started without its approval. It is evident that, especially with minor patients, a certain number of ethical requirements has to be met before undertaking an investigation.

- It must be impossible to acquire the same information by performing the study on adults. Since it is known that the course of IDDM in adults may be milder, certainly during the first years, this study on the remission phase has to be done with minors.
- Parents and children, taking into account their age and ability to understand, must be well informed on the positive and the negative aspects of participation.

This study starts at a most awkward moment for both patients as well as parents. Ethically it would be preferable to provide a written summary of the study, its purpose, the advantages and the disadvantages, before treatment is started. Due to the nature of this study, however, a summary can only be presented some time after the decision to participate in the study (Appendix I). A letter with signature as an indication of knowledge of and understanding about and consent to participation in the study are returned to the researcher.

Both at the start of the study and in the letter it is emphasized that participation may be stopped at any time during the study without explanation. It is stated explicitly that a refusal to (further) participation will not influence the relationship between patient and physician. In that situation, however, pump treatment will only be continued in case it is evidently better

for this particular patient and when the financial support for this treatment is taken over by either the insurance company or the parents themselves. Otherwise, the patient will start with conventional injection therapy.

The end of the study may pose another problem. The costs of CSII are considerable (Appendix II). It is not certain that all insurance companies will provide financial support. The study budget is not sufficient to provide financial support after the two years of the study. This implies that refusal by the insurance company will result in either a change of treatment or in considerable financial burdens. Considering the possible benefit with regard to the acute and late complications of IDDM, however, the costs of pump treatment may cost the insurance companies less in the long run.

FEASIBILITY AND PSYCHOLOGICAL TESTS

Feasibility

Since CSII has never been used in not selected newly diagnosed diabetic children, an investigation into the feasibility and the psychological impact of the therapy is an important facet of this study.

With feasibility not only the practicability of the started treatment is meant, but also the potentially improved quality of life. Although it is especially difficult to evaluate the latter, following aspects have been studied:

- Acceptation of the therapy by parents and child
- Practical problems of CSII
- Frequency of phone calls for advice
- Frequency of home visits by the nurse practitioner

The child and the parents are explicitly asked to give the diabetes team their opinion on the therapy. Problems are openly discussed in order to evaluate carefully whether continuation of the treatment is justified. Practical problems with the pump treatment can result in a metabolic disregulation. This may be caused by pump failure or by inadequate handling of the pump by the patient or his parents. If these problems are caused through inadequate handling of the pump on purpose, CSII treatment has to be terminated.

The frequency of telephone calls to the diabetes team can be used as an indication of the complexity of the treatment. It provides information on the frequency with which consultation is needed with respect to adjustments in insulin dose and/or diets, in special situations or during intercurrent infections.

Sometimes parents will contact the nurse practitioner when pedagogical or psychological problems with their child arise.

With respect to the telephone calls, the patients (and/or parents) are divided in 3 categories:

- contacting the nurse practitioner 1 time per month or less
- contacting the nurse practitioner 2 - 5 times per month
- contacting the nurse practitioner more than 5 times per month

Home visits by the nurse practitioner, after the initial instruction period can be divided in four groups:

- to instruct new skills (other injection sites)
- refresher courses before holidays, a check of already acquired skills
- instruction to schoolteachers, trainers etc.
- home visits to discuss psychological or pedagogical problems

These home visits, their purpose and frequency, provide important information about the burden and the feasibility of CSII treatment in newly diagnosed children. After 1 year the 2 groups (CT and CSII children) are compared with respect to these parameters in order to gain an impression of the feasibility of CSII treatment.

Psychological tests

To compare the psychological impact of the two therapies, the children are tested psychologically at the end of the study, 2 years after the clinical onset of the disease. The children are tested by dr Slijper and Mrs Kicken (Dept. of Child Psychiatry, Erasmus University and Dijkzigt Hospital/Sophia Childrens' Hospital, Rotterdam.

In collaboration with dr Slijper several general tests - stated below - have been selected to evaluate certain aspects of the child's personality and its relation with its family (and vice versa). The test scores of the 2 groups are compared with each other. (If reference scores are available the scores of each group are also compared with these scores). Two questionnaires (5, 6) have been designed specifically for this study.

1. Wechsler Intelligence Scale for Children (WISC)
2. Junior-Dutch Personality Test
3. Family Relation Test
4. Family Environment Scale
5. Diabetes Questionnaire
6. Assessment of Acceptation Scale.

Of the WISC only the vocabulary subtest and the block design subtest have been performed to obtain some information on the intelligence. For youngsters (< 4 years) a modified test (WIPPSI) has been used, providing comparable scores.

The Dutch Personality Test for Juniors provides information on several aspects of the personality of the children (Bucking 1975). The items are summarized in Appendix III. The test is only suitable for children of 9 years and older.

The Family Relation Test quantifies the negative and positive feelings of the child towards his family (parents and siblings). It also reflects the feeling of the family towards the child, as experienced by the child! Children of 4 years of age and older can participate in the test.

The Family Environment Scale gives a reflection on "family life" as observed by the different members of the family. The items are given in Appendix IV. The parents of the children have been requested to answer the questionnaire belonging to this test, either in the hospital or at home.

The Diabetes Questionnaire has been designed specifically for this study. The 58 questions (Appendix VI) provide information on 9 items, shown in Appendix V.

This test is directed specifically at the two treatments, their influence on every-day life with possible consequences for the behaviour of the child and his coping responses.

The Assessment of Acceptation Scale consists of 5 questions (Appendix VII), concerning acceptation, metabolic regulation, physical and psychological well-being and the compliance of parents and child to effectuate a given advice. The parents and 3 members of the diabetes team are independently requested to answer these questions. The scores given are from very good towards poor from 1 to 5. Equality of assessments or incongruity will give important information. It is evident that a negative (high) score of this test by all persons suggests more problems than only a negative score of one reviewer.

If psychopathology is observed during the tests further contact will be sought in that particular case in concert with the diabetes team.

METABOLIC CONTROL

The goal of the treatment of IDDM is achieving near normoglycaemia, no symptoms of hypo- or hyperglycaemia and a normal development (in this context: physical development). To evaluate in how far CSII treatment contributes to achieving this goal compared to the conventional injection therapy, the following parameters have been chosen:

- stable HbA1 (sHbA1)
- home measured blood glucose values and hypoglycaemia
- intermediary metabolites, to wit lactate, pyruvate, 3-OH-butyrate, triglyceride and non-esterified fatty acids (NEFA), branched amino acids
- cholesterol and HDL-cholesterol
- normal physical development

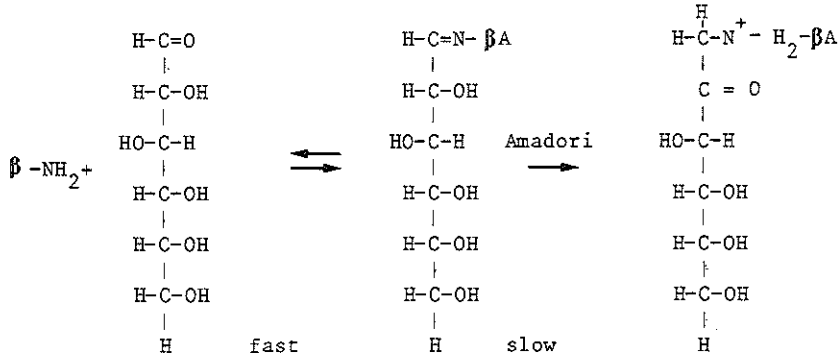
Stable HbA1, most intermediary metabolites, cholesterol and HDL cholesterol have been determined by the Department of Clinical Chemistry, Erasmus University and University Hospital Rotterdam (Head of Dept.: Prof. dr B. Leynse). The amino acids have been measured by the Metabolic Laboratory of the Sophia Childrens' Hospital, Rotterdam (head of Lab.: Ir W. Blom).

Although the insulin dose is strictly speaking no parameter for the metabolic control, it is mentioned in this paragraph because of its close relationship to the metabolic control.

sHbA1

Stable glycosylated hemoglobin is the principal parameter for the glycaemic control. The introduction by Koenig and others of sHbA1c as a parameter for the integrated glycaemia over the previous 3 to 4 weeks, has lead to the use of it as a clinical tool for diabetes control (Koenig 1975, Monnier 1982, Goldstein 1984). The velocity of the reaction depends on the blood glucose concentration and the span of exposure of hemoglobin to this concentration. Total sHbA1 is formed through condensation of a molecule of glucose with the amino terminal valine of the betachain of hemoglobin and represents the major component of total sHbA1, measured throughout this study. This reversible reaction (shown in figure 4.1) is followed by the irreversible "Amadori" rearrangement to form a stable ketoamine. The formation of HbA1c is a non-enzymatic reaction.

Figure 4.1 The formation of SHbA1c



Changes in sHbA1c in the patients are assessed by the measurement of sHbA1 once every month.

An electrophoretic method for the determination of sHbA1 has been used. This method is unaffected by variations in temperature or minor variations in pH of ionic strength of the buffer (Menard 1980). To measure the sHbA1 percentage of total Hb, 0.5 ml of whole blood is incubated overnight at 37 C in excess saline 0.15 mol/l. Erythrocytes are collected by centrifugation, lysed and applied onto an agarose gel (Corning, New York, USA). The sHbA1 fraction is separated by electrophoresis. After drying, the percentage is measured by direct scanning at 420 nm. Every value is the mean of a duplicate measurement. The inter assay variation coefficient (SD: X. 100%) in the lower range (sHbA1 : 6.8%) is 8% and in the higher range (sHbA1 : 13.2%) is 3.9%. The reference interval (mean ± 2 SD; 42 non-diabetic children, visiting the outpatient clinic for minor problems, range of age: 1 - 20 years) for sHbA1 with this method is 5.4 - 9.0%.

Home measured blood glucose levels

As previously mentioned, a frequency of 3 to 5 measurements per week is recommended for blood glucose measurements at home. All patients and/or parents receive a "diabetes diary" to note all blood glucose values, special situations and diabetic symptoms etc.. The blood glucose measurements are used primarily for an adequate and fast adjustment of insulin and/or diet. Since these controls are performed at different hours of the day and for different reasons, it will be difficult to compare these home measured blood glucose levels. It is relevant to calculate the mean frequency of determinations per 28 days in the two groups.

Besides information obtained from diaries, insurance companies have been approached by letter (Appendix VIII) to provide information, if possible, on the quantity of blood test strips refunded by them.

It is imperative to know the incidence of low blood glucose

levels ($\leq$ 2.2 mmol/l), since it has been suggested that CSII may result in a higher frequency of hypoglycaemic periods (KROC study group 1985, Arias 1985). Hypoglycaemia is classified in 2 groups:

1. hypoglycaemia with unconsciousness, requiring glucagon or glucose i.v.;
2. blood glucose levels of 2.2. mmol/l or lower and/or subjective hypoglycaemic symptoms, to wit dizziness, altered consciousness, aggressive behaviour, trembling and sweating.

From the diaries the mean frequency (per month per group) of these forms of hypoglycaemia is determined. Whether or not hypoglycaemia has occurred the month previous to the hospital visit is noted each month in the records of the patients. These records have also been used to obtain information on the occurrence of hypoglycaemic periods.

Intermediary metabolites

Blood lactate and pyruvate, intermediary metabolites of the carbohydrate metabolism, are increased after a longer period of insufficient insulin effect (Cherrington 1982) thus providing information concerning chronic metabolic disregulation. They have been measured after an overnight fast 6 and 12 months after the onset of IDDM. After immediate deproteinization of the venous blood samples lactate and pyruvate concentrations have been determined by spectrophotometry (Bergmeyer 1974 1,2) using the COBAS BIO (Hoffman-LaRoche, Basel, Switzerland). Results are given as the mean of 2 measurements. The reference interval for lactate is < 3.0 mmol/l for newborns and 1.0 - 2.0 mmol/l for children and for pyruvate (for children of all ages) it is 40 - 70 µmol/l.

Triglyceride, NEFA and 3-OH-butyrate concentrations supply information concerning the lipid metabolism. Increased lipolysis as a result of insufficient insulin levels, leads to an increase in NEFA and 3-OH-butyrate levels. Triglyceride concentration will also increase during a period of insulin deficiency. Because of the high sensitivitiy of fat cells for insulin, even a small residual insulin production can reverse these effects (Madsbad 1979). Triglyceride, 3-OH-butyrate and NEFA concentrations are measured by spectrophotometry (Bergmeyer 1974 3,4), using the COBAS BIO (Hoffman-LaRoche, Basel, Switzerland). Results are given as the mean of 2 measurements. Reference intervals for triglyceride, 3-OH-butyrate and NEFA are for children respectively < 2.29 mmol/l, 0.06 - 0.2 mmol/l and 0.5 - 1.2 mmol/l.

It is suggested that insulin promotes the uptake of the branched amino acids (leucine, isoleucine and valine) by muscle as well as exerts an inhibitory effect on the release of peripheral amino acids (Stryer 1981). Branched amino acids have been determined 6 and 12 months after the onset of IDDM. The amino acids analysis has been performed with an LKB 4151 Alpha Plus R Amino Acid Analyzer (LKB, Cambridge, England). The results are the mean of 2 measurements. Reference intervals for leucine, isoleucine

and valine are for infants and children respectively 0.045 - 0.155, 0.026 - 0.094 and 0.057 - 0.262 mmol/l (Soupart 1962).

HDL cholesterol and Cholesterol

Higher cholesterol and HDL cholesterol levels have been demonstrated in diabetic children compared to healthy controls (Ewald 1984). As discussed by Nikkila, this might be associated with an increased concentration of circulating insulin (Nikkila 1981). Taking into account one of the major complications of IDDM - atherosclerosis - it seems justified to study whether the treatments differ with respect to these factors.

Cholesterol and HDL cholesterol have been determined every 2 months. Total serum and HDL cholesterol have been measured by the enzymatic CHOD-PAP method (Boehringer, Mannheim, FRG). Results are given as the mean of 2 measurements. Reference intervals for cholesterol and HDL cholesterol are respectively for children 3.57 - 6.25 mmol/l and 0.62 - 2.09 mmol/l.

Physical development

The growth of the child is followed by measuring height and weight during each visit to the outpatient clinic. This is noted on the growth charts (weight for height) for Dutch children (Van Wieringen 1972) and results in a percentile along which the child is growing. Data of the growth before the onset of the disease (at least 6 months before) are obtained through the parents from the "Baby and Toddler Clinics". It is assumed that the child will usually continue to grow after the start of an adequate insulin administration along the same percentile level as before the onset of IDDM (again at least 6 months before). When gross differences from this percentile are found, they may point to a chronic metabolic disregulation (deflection towards a lower percentile) or an "over"treatment (increase towards a higher percentile). Both necessitate extra attention of the diabetes team to elucidate the possible cause.

The exogenous insulin administration

The insulin dose is noted at each visit to the Diabetes Clinic in the patients' records. It is expressed in units per kg bodyweight per 24 hours. The moment at which the dose exceeds 0.5 U/kg bodyweight/24 hours is considered to be the end of the remission period with respect to the insulin dose.

ENDOGENOUS INSULIN RESERVE

The estimation of the endogenous insulin production is one of the principal parameters of this study. The C-peptide secretion, stimulated by 1 mg (i.v.) glucagon, is a widely accepted method

to study the endogenous insulin reserve in insulin dependent diabetic patients (Faber 1977, Hendriksen 1977, Madsbad 1981). This test which frequently induces nausea and vomiting is rather traumatic for children. Hence, it can not be used to follow the endogenous insulin secretion at frequent intervals.

Provided that the integrated plasma C-peptide levels and the C-peptide concentration in 24 hours urine correlates well, 24 hours urinary C-peptide excretion may serve as a measure for the activity of the beta cells during a 24 hours' day (Meistas 1981). Before using this parameter we have studied the relationship between the 24 hours urinary C-peptide excretion and the plasma C-peptide levels during the glucagon stimulation test and after an overnight fast.

First the method is described according to which plasma and urinary C-peptide levels are determined. The C-peptide determinations have been performed by the Department of Clinical Chemistry, Erasmus University and University Hospital Rotterdam. This is followed by a comparison of the 2 methods. Finally reference intervals for the 24 hours urinary C-peptide levels in healthy children are estimated, obviously necessary to interpret the data obtained from diabetic children.

Methods

After collecting blood samples in heparinized Vacutainer tubes, the samples are placed on ice. Shortly thereafter the samples are centrifuged. Plasma samples are stored below -20° C until assay within a fortnight.

Urine is collected at home during 24 hours. Every voiding is frozen immediately in the freezing part of the home refrigerator (-8° C or less). The urine samples for the C-peptide measurement are processed under the same conditions as the plasma samples.

Plasma C-peptide and urinary C-peptide levels are determined in the same assay according to the method described by Heding, using the antibody M1230 (NOVO, Bagsvaerd, Denmark) (Heding 1975). All samples are pretreated with PEG-6000 (Merck, Darmstadt, FRG) to a final concentration of 12.5% to remove possible antibody bound (pro)insulin. Then they are centrifuged. An adaptation of the original procedure is the completion of the separation of bound and free C-peptide performed by precipitation with PEG-6000 (final concentration 15%) instead of ethanol. A study of 30 plasma samples containing significant amounts of C-peptide showed no difference in PEG pretreatment directly after sampling or after storage of untreated samples below -20° C (for maximally 14 days) and pretreatment just prior to C-peptide determination. Human albumin (Behringwerke, Marburg, FRG) in phosphate buffer 0.04 mol/l, pH 7.4, was added to all urine samples until 6% (w/v), in order to avoid matrix induced differences between serum and urine samples. From each sample dilutions 1:3, 1:11 and 1:33 were made. Upon dilution the urine samples thus treated showed good parallelism. As the standard curve encompassed 0.01 to 0.25 nmol/l C-peptide urine samples, diluted up to a concentration of approximately 0.15 nmol/l, are taken to calculate the C-peptide

concentration in the original urine sample. In this way the most accurate part of the standard curve is sought.
The lower limit of sensitivity in our assay (expressed as c.p.m. for zero standard and 3 SD) is 0.02 nmol/l for plasma samples and 0.06 nmol/l for (at least threefold diluted) urine samples.

For plasma samples the intra assay coefficient of variation (cv) is 7% in the lower range (0.19 nmol/l), 4% in the middle range (0.38 nmol/l) and 5% in the upper range (0.56 nmol/l) respectively (n=9). For urine samples the intra assay cv is 14% (0.13 nmol/l), 3% (2.6 nmol/l) and 4% (12 nmol/l) respectively (n=10). The inter assay cv's for plasma samples are 26% (0.09 nmol/l, n=20), 6% (0.42 nmol/l, n=20) and 7% (0.68 nmol/l, n=13). The inter assay cv's for urinary samples are 17% (0.16 nmol/l, n=38), 9% (2.7 nmol/l, n=42) and 11% (13.8 nmol/l, n=39).

Comparison of plasma and urinary C-peptide levels

In order to evaluate the relationship between plasma C-peptide levels after an overnight fast, during the glucagon stimulation test and the 24 hours urinary C-peptide excretion the 30 participating children have been tested and have collected 24 hours urine, as previously described. It is assumed that the children maintain their usual insulin regime, diet and level of activity during each collection period.

The glucagon stimulation test has been performed in the hospital. The morning of the test the children have arrived fasting at the hospital at 8.00 a.m.. On admission an indwelling intravenous catheter (22G) has been inserted through which blood sampling has taken place. Its patency has been maintained by flushing with saline 0.15 mol/l with 50 units of heparin/ml saline after each blood sample. At 15 and 0 minutes before and 6, 15, 30 and 45 minutes after a slow intravenous injection of 1 mg glucagon ® (NOVO, Bagsvaerd, Denmark) blood samples have been taken to measure the C-peptide and glucose concentrations. Blood samples are kept on ice until further processing is carried out, as previously described. Within one week of the glucagon stimulation test (but with at least a 24 hours difference) the 30 children have collected at home 24 hours urine, freezing each voiding immediately.

Plasma C-peptide values obtained during the glucagon test are expressed as the area under the curve, taking the X-axis as lower limit.

The plasma C-peptide concentrations during the glucagon stimulation, expressed as area under the curve (AUC) and the fasting plasma C-peptide levels show a significant correlation with the C-peptide excretion in 24 hours urine (nmol/24h) with $r=0.83$ ($p < 0.001$) and $r=0.83$ ($p < 0.001$), respectively figure 4.2a and 4.2b.

This correlation indicates that the stimulation of beta cell activity in insulin dependent diabetic children by glucagon administration and under 'normal life' activities and meals results in comparable C-peptide values. The relationship between 24 hours urinary and fasting plasma C-peptide concentrations sug-

gest that the beta cells are also stimulated during the early morning. This may be ascribed to the increased insulin 'need' or decreased insulin sensitivity during the early morning (Campbell 1985).

Apparently, different hyperglycaemic stimuli, resulting in the 24 hours urinary and fasting blood C-peptide levels, provoke a comparable and probably maximal activity of the residual beta cells.

Glucagon administration also results in a stimulation of the residual beta cells. Both ways of stimulation therefore appear to result in a maximum activity of the beta cells, although effectuated by different mechanisms.

Thus the measurement of 24 hours urinary C-peptide levels seems to be a reliable and non-traumatic method to estimate beta cell activity. In the pump study the children have collected 24 hours urine once a month (before or just after their visit to the hospital). Because the mechanisms of stimulation probably differ, the glucagon stimulation test has not been entirely stopped. It has been conducted after 6 and 12 months.

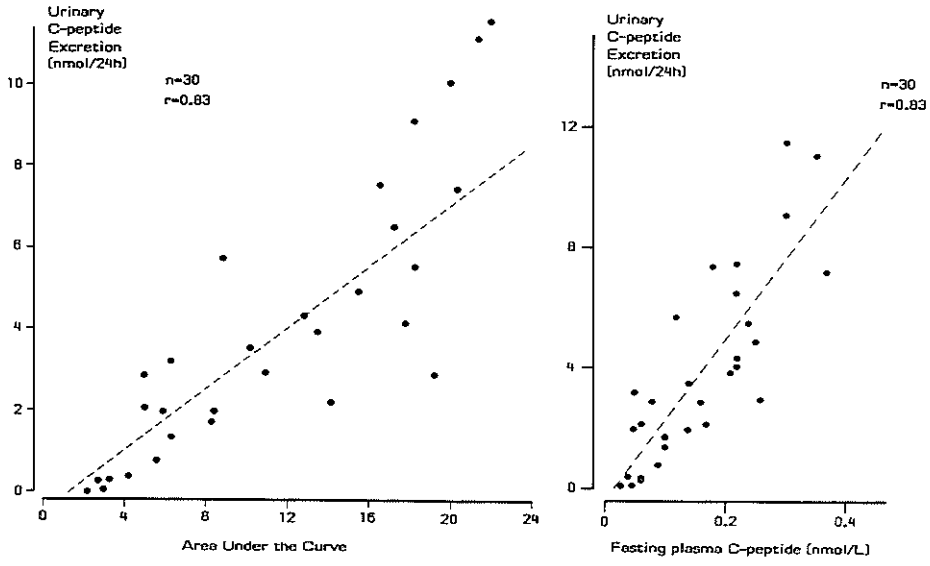


Figure 4.2a and 2b The relationship between the 24 hours urinary C-peptide production (nmol/24h) and
- stimulated plasma C-peptide values, expressed as area under the curve (AUC) (2a)
- fasting plasma C-peptide values, expressed as nmol/l (2b)

in 30 insulin dependent diabetic children

Estimation of reference intervals

For the interpretation of the 24 hours urinary C-peptide excretion with regard to the different ages of the diabetic patients, reference intervals have to be estimated. Control data have been obtained from 30 healthy siblings (8♀, 22♂). These children have a normal sHbA1 percentage, no islet cell antibodies nor any other relevant disease. To observe the physiological variation in urinary C-peptide excretion, 19 of these siblings have collected 24 hours urine once every 5 to 7 weeks during 1 year. Eleven children have collected 24 hours urine 3 times. Informed consent has been obtained from the parents of all participating children, according to the Helsinki Declaration.

The statistical analysis of the control group data comprises analyses of variance, segregating variability between children (c), between sampling days (d) and the residual variability (within) children and the intra assay variability (r). Analyses of variance are performed using a special computer program (GLIM) to take account of the fact that the urine samples of the 30 children could not always be assayed within the same batch and therefore could be considered randomly distributed between assay-batches (Baker 1978). Since the data have been obtained from RIA calibration curves using a logscale, the data as recorded (nmol/24h) are transformed to logarithms before executing the analysis. The results of the analysis of variance of all sibling data are given in table 4.VI.

Table 4.VI Analysis of variance of sibling data

Source of variation	Degrees of freedom	Mean square	Expected variance components	Individual components of variance
between children	29	0.401	$\sigma_r^2 + 7\ \sigma_c^2$	$\sigma_c^2 = 0.052$
between days	41	0.058	$\sigma_r^2 + 30\ \sigma_d^2$	$\sigma_d^2 = 0.001$
residual	139	0.038	σ_r^2	$\sigma_r^2 = 0.038$

Clearly residual variability (mainly physiological - within children - variability) and variability between children contribute most to overall variability. The variation between assay days is negligible. In order to investigate whether part of the variability can be explained by variation in age, a scatter plot has been drawn (figure 4.3). To take this relationship between age and urine C-peptide excretion into account, the method of segmented regression is applied to derive regression equations: mean log (Urinary C-peptide excretion) = 0.19 + 0.089 age (upto 10 years); mean log (Urinary C-peptide excretion) = 1.084 ($\geq$ 10 years) (Draper 1981).

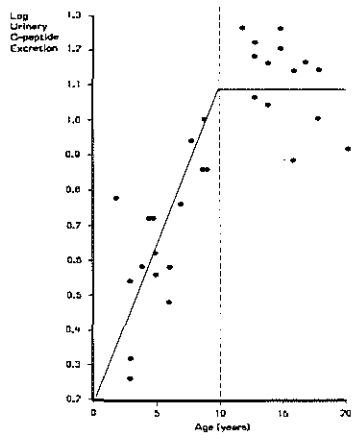


Figure 4.3. Scatter plot of logarithms of C-peptide excretion data (nmol/24h) against age (years) for 30 healthy siblings; each point represents the mean of 3-10 monthly determinations. Regression lines fitted according to segmental method are shown.

The estimated components of variance ($\hat{\sigma}_c^2$, $\hat{\sigma}_d^2$ and $\hat{\sigma}_r^2$) and the estimated regression equations are used to derive estimates of reference intervals for the urinary C-peptide excretions. These reference intervals are estimated as

predicted mean + factor times standard deviation.

The factor depends on the desired amount of coverage of the population and on the degree of confidence that this amount (or more) will be covered (Geigy 1968). Given the number of individuals on which the present regression equations are based this factor is K = 2.2, so that on average 95% of the population studied is covered. The standard deviation is derived from the estimated components of variance, taking into account the number of independent replicate determinations (n) per individual, according to the formula:

$$(\text{standard deviation})^2 = \frac{\hat{\sigma}_r^2}{n} + \frac{\hat{\sigma}_d^2}{n} + \hat{\sigma}_c^2$$

The estimated reference intervals are given in table 4.VII

Table 4.VII 95% Reference interval for C-peptide excretion values, applying to various conditions

Age (yrs)	Predicted mean logscale	nmol/24h	Number of replicates per individual (n) 1	2	3	5	10
2	0.368	2.3	0.7- 7.8	0.9- 6.1	1.0- 5.5	1.1- 5.0	1.2- 4.6
4	0.346	3.5	1.0-11.8	1.4- 9.1	1.5- 8.2	1.6- 7.5	1.8- 7.0
6	0.724	5.3	1.6-17.8	2.0-13.7	2.3-12.4	2.5-11.3	2.7-10.5
8	0.902	8.0	2.4-26.8	3.1-20.7	3.4-18.7	3.7-17.1	4.0-15.8
⩾10	1.034	12.1	3.6-40.7	4.7-34.5	5.2-28.4	5.7-25.9	6.1-24.0
standard deviation (logscale)*			0.239	0.188	0.168	0.150	0.135

$$* \ (SD)^2 = \frac{0.043}{n} + 0.014$$

For easy interpolation they are also shown in graphical form (figure 4.4.). These results indicate that the actual reference limits will narrow by a factor of about 2 when means of excretion values from 5 independent samplings are considered instead of a single determination. There is a considerable variation in UCP per child. This is not unexpected since these reference values, obtained in healthy siblings, will probably not represent a maximally stimulated endogenous insulin production, as is more likely to be the case in diabetic children. The linear increase in urinary C-peptide excretions from 2 to 10 years emphasizes the importance of taking age into account when evaluating the urinary C-peptide excretion in children.

In the pump study the urinary C-peptide excretion will be expressed as a percentage of the predicted mean value (UCP), according to the age of the child (calculated for each month).

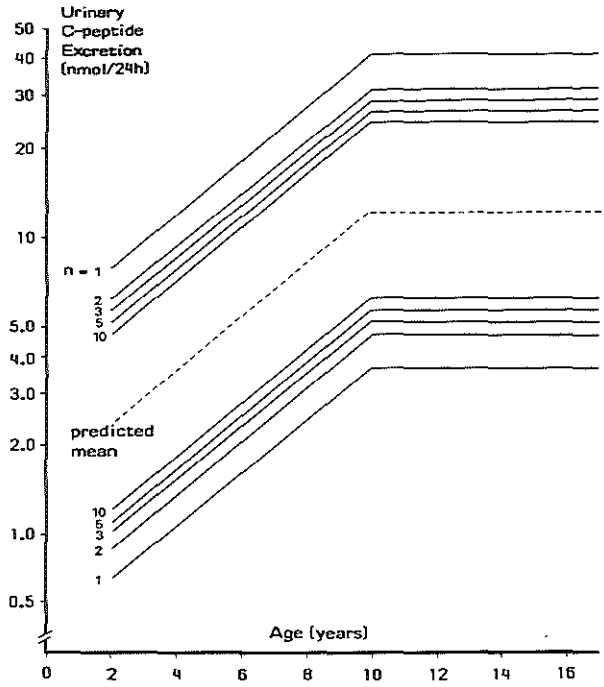


Figure 4.4. Nomogram for the estimation of 95% reference interval for the urinary C-peptide values (nmol/24h) based on replicate measurements.

IMMUNOLOGICAL PARAMETERS

The following antibodies have been included in order to observe their possible influence on the residual beta activity after clinical onset of IDDM:

- islet cell cytoplasmic antibodies (ICCA)
- islet cell cytoplasmic antibodies, which are complement fixing (ICCA-CF)
- islet cell surface antibodies (ICSA)
- anti insulin antibodies IgGIa
  anti insulin antibodies IgGIb

Islet cell cytoplasmic antibodies are detected with indirect immunofluorescence assays on sections of a fresh frozen human blood group 0 pancreas as described in detail by Marner and co-workers (Marner 1983). They have been measured by the Department of Clinical Immunology, (dr Molenaar, Stichting Samenwerkende Delftse Ziekenhuizen, Delft). The results are given in a semi-quantitative scale, varying from negative (0) towards highly positive (4+). Blood samples are assayed at onset and after 6 and 12 months.

For the detection of islet cell surface antibodies (ICSA) in the sera of the diabetic children viable rat islet cells are used. Indirect immunofluorescence is used to demonstrate the binding of human antibodies to rat islet cell membranes. A more detailed description of the assay is given by Van de Winkel (Van de Winkel 1982). The patients' samples have been kindly tested at onset and after 6 and 12 months by the Department of Clinical Research, (Head of Dept.: Prof. D. Pipeleers, VUB, Brussels, Belgium). The results thus obtained are also given in a semiquantitative scale, varying from negative (0) up to highly positive (4+).

To study the antibody production in the participating children before the start of insulin therapy and 3, 6, 9 and 12 months later, insulin antibody levels have been kindly determined by NOVO Research Laboratory (Bagsvaerd, Denmark) according to the method of Christiansen (Christiansen 1973). These form the classic insulin antibodies (IgGIa).

The presence of anti insulin antibodies before the start of insulin therapy (IgGIb) has also been checked by a more sensitive method. Blood samples of our patients taken before the start of the therapy have been kindly tested by the Hagedorn Research Laboratory (dr C. Binder, Gentofte, Denmark). The detection of the antibodies has been performed by means of a sensitive, modified PEG-assay (Lauritzen 1982). Non-specific binding is subtracted. This implies that positive figures indicate a significant and specific binding.

STATISTICAL ANALYSIS

The results are given as mean $\pm$ 1 standard error of the mean (SEM))

sHbA1, UCP and insulin dose

The statistical analysis has been performed in close collaboration with Professor Van Strik (Department of Biostatistics, Erasmus University Rotterdam, Rotterdam).

Three parameters, sHbA1, UCP and the insulin dose have been studied inter alia. To facilitate the evaluation of these data with respect to each other as well as with respect to the two groups, several characteristics have been calculated for each of these parameters.

The sHbA1 values have been plotted against time. Following aspects are studied: increasing or decreasing trend in time, the variability of sHbA1, as an indication for the stability of

metabolic control, the course of sHbA1 and the breakpoint after which the sHbA1 increases significantly compared with previous determinations.

To approximate the decreasing or increasing trend, without an assumed normal distribution and minimizing the influence of extreme values, a median straight line is drawn through the plotted points. This means that before and after the median value on the X-axis respectively the same numbers of values are situated above and below the line (Brown 1951, Mood 1950). The slope of this line (henceforth called Mood line) provides an estimate of the trend that describes the course of sHbA1 values in time. Since the first two values of sHbA1 (at onset and after 1 month) are affected by the previous period (before the onset) these points are not included.

Not only the trend but also the level of sHbA1 is relevant. The value on the Mood line after one year (influenced by all previous points), has been chosen to characterize, in addition to the slope, the course of sHbA1.

The degree of variation around the Mood line is characterized by the number of crossings of subsequent points above and below the Mood line in relation to the total number of points (variability index).

Three successive sHbA1 values above 9.0% are considered to characterize the end of the remission period regarding the metabolic control. The first of these 3 successive points in time at which the sHbA1 exceeds 9.0%, is considered to be the breakpoint and therefore the end of the remission period with respect to the metabolic control. Finally the sHbA1 value at onset is used as parameter for the metabolic disregulation. Hence, the sHbA1 course is characterized by the following factors:

- the initial sHbA1 level - as parameter for the metabolic disregulation
- the slope of the Mood line
- the sHbA1 value on the Mood line after one year of IDDM
- the variability index
- the first moment of three at which a sHbA1 above 9.0% is measured.

For the course of UCP the same methodology as described above is used. As discussed previously, the urinary C-peptide values are given as percentage of the predicted mean for a certain age (age is expressed in years + months). These percentages are plotted against time. Criteria for the evaluation of the UCP course is the presence or absence of a significant increase of UCP after the start of the treatment, its maximal value, the speed of the decrease, the (predicted) moment at which no UCP can be detected anymore and the variability in UCP. First the Mood line is drawn through the plotted dots, as described above, taking account of all determinations. Sometimes it is not possible to draw this line through all points, because of a considerable increase of UCP after the onset, henceforth called "a peak". This peak is characterized by a maximal value and the point in time at which

it terminates. In these cases the line will be drawn from this turning point onwards.

The assessment of the presence of a peak has been performed by two observers. One of the observers has received the plotted data, without knowledge of the patients and their treatments. If UCP is still detectable after 1 year, extrapolation of the line towards UCP = 0 provides information on the predicted point in time at which no UCP will be present anymore.

The variability index for UCP is, similarly as for sHbA1 characterized by the number of crossings in relation to the number of determinations. Thus, the UCP course is characterized by the following factors:

- the initial UCP
- the maximal UCP
- (in the presence of a peak) the end time of the peak
- the slope of the Mood line
- the (predicted) point in time at which no UCP can be calculated anymore
- the variability index.

The insulin dose usually increases gradually. The moment at which the dose exceeds 0.50 U/kg bodyweight/24 h marks the end of the remission period with respect to the insulin dose. Hence, this parameter will be characterized by the following aspects:

- the increase of the dose during the first year
- the frequency and the size of the increasing steps
- the point in time at which the dose exceeds 0.50 U/kg bodyweight/24 h.

Psychological tests

To evaluate whether in the psychological test "Assessment of Acceptation" the opinions of the 5 reviewers are in agreement, the test of Friedman has been applied (De Jonge 1983 1). If the hypothesis "the various observations of the different reviewers are not in agreement" is rejected, the scores of the different reviewers for each child can be added. This has the advantage that the scale of this assessment test increases from 1-5 to 5-25.
This increased diversity of the results may allow a better comparative evaluation of the two groups.

Comparison of the two groups: CSII versus CT

The two-sided test of Wilcoxon (or U-test of Mann & Whitney) is applied to compare the two groups of patients with respect to quantitative data at significance level of $\alpha = 0.05$ (De Jonge 1983 2). The Chi-square test (for a 2 x 2 Table) is used to evaluate the differences between the two groups with respect to binary observations (De Jonge 1983 3). Finally, the test of Yates

and Cochran has been applied to analyse the semiquantitative data (De Jonge 1983 4).

Relationship between the different parameters

To determine whether an association exists between the time courses of UCP and sHbA1 the Pearson contingency coefficient is determined (Sachs 1978).

For the evaluation of the relationship between the different parameters the Spearman coefficient of correlation (r_s or r) is calculated (De Jonge 1983, 3).

An P value < 0.05 is considered to indicate statistical significance. To evaluate differences between 2 coefficients the Spearman coefficient (r_s) must be transformed into a Pearson coefficient (r_p), since no test has been developed yet to analyse the difference between 2 Spearman coefficients. The Pearson coefficients are transformed in a Z value according to the following formula: ($Z = 1.1513 (\log (1 + r_p) - \log (1 - r_p))$. The statistic Z is standard normally distributed.

The transformation of r_s to r_p may be performed according to the formula: $r_p = 2 \sin 1/6 \pi . r_s$, with 2 assumptions. These assumptions, a binormal distribution and sufficiently large random samples (>30) are (probably) not fulfilled. This implies that if no significant difference is found it is highly unlikely that the difference may become significant in other tests, specifically developed for Spearman coefficients.

SUMMARY

The study design and protocol and the parameters chosen for the pump study are expected to supply answers to the following questions:

1. Is CSII feasible in previously randomized newly diagnosed diabetic children? What is its psychological impact?
   - Are CSII-treated children and/or their parents requiring more attention from the diabetes team, and in particular from the nurse practitioner?
   - Are the treatment and its consequences accepted by the child and its family?
   - Are the problems caused by the therapy acceptable?
   - Is it reducing possible effects of IDDM on the personality and the social contacts of the child?

2. Does CSII improve the metabolic control of insulin requiring diabetic children?
   - Do the CSII treated children achieve a better metabolic control or even near normoglycaemia?
   - Does the metabolic control remain better (or near normal) during a longer timespan.

- Does CSII treatment result in a more stable metabolic regulation, reducing the frequency of necessary blood glucose measurements at home?
- Do CSII treated children need smaller insulin doses? Is their dose adjusted more frequently with smaller amounts?

3. Does CSII prolong the remission period and is it possible to elucidate which factors contribute to the effect of CSII on the remission phase. Can some factors be excluded to exert a (direct) influence on it?
   - Is CSII resulting in a larger UCP during a longer period of time?
   - Is the slope of the UCP path less steep in CSII treated children?
   - Can a distinct association be demonstrated between the courses of sHbA1 and UCP?
   - Is the occurrence and duration of the remission period related to characteristics of the patients (HLA type, metabolic disregulation, age)? Can a relationship be shown between these characteristics and the individual parameters of the remission?
   - Or can an association be demonstrated between the presence of immunological disturbances (ICCA, ICCA-CF, ICSA, IgGIa or IgGIb) and the remission period?
   - Does CT or CSII treatment induce a different production of insulin antibodies (IgGIa), using human insulin in both groups?

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CHAPTER 5

RESULTS OF THE PUMP STUDY

INTRODUCTION

From November 1981 until June 1984 34 newly diagnosed diabetic children have been referred to the Sophia Childrens' Hospital. Thirty participate in this prospective study and have started at random with either CSII or CT.

The first paragraph of this chapter deals with the characteristics of the children participating in the study. Subsequently results of one year of follow-up are given. As mentioned previously, the results of the psychological tests are incomplete as the children are tested only after two years. As a result a total of 15 children has been tested psychologically so far (6 children with CSII and 9 with CT treatment). The chapter ends with a summary.

CHARACTERISTICS OF THE PARTICIPATING CHILDREN

The characteristics of the 30 children who entered with informed consent this study, are given in table 5.I. Each child will be identified by a number in the subsequent text (1-15 for the CSII group and 16-30 for the CT group).

Table 5.I Characteristics of the participating children

CSII patients						CT patients					
patients	age at onset (yrs)	sex	HLA Dr		socio-economic class	patients	age at onset (yrs)	sex	HLA Dr		socio-economic class
1	10.9	M	4	6	2	16	3.1	M	4	3	5
2	16.8	M	4	3	6	17	4.8	F	4	3	6
3	12.3	M	2	3	6	18	12.3	F	3	3	3
4	13.9	F	4	3	6	19	8.8	M	4	2	3
5	10.3	F	5	3	4	20	11.8	F	1	8	6
6	13.2	F	7	3	2	21	11.1	M	4	4	2
7	3.0	M	4	8	6	22	6.9	M	4	1	3
8	7.2	F	4	3	5	23	5.1	M	6	3	6
9	5.8	M	4	1	5	24	4.5	F	9	3	5
10	7.6	F	1	3	5	25	4.3	F	4	3	3
11	11.5	F	4	3	2	26	4.2	F	4	3	6
12	12.5	F	4	6	6	27	11.6	F	4	4	6
13	6.0	M	3	3	6	28	4.8	M	6	3	2
14	1.9	M	3	3	6	29	10.2	F	4	4	4
15	9.6	M	4	3	3	30	1.8	M	4	2	6

Of the 34 originally referred children 4 "dropped out". One Moroccan child has not been treated as planned with CSII because she had already started manipulating the pump in the hospital. This together with the language problem has necessitated the decision to terminate CSII treatment. Two children, 5 and 2 years old respectively, have started with CT instead of the planned pump treatment because of their age at onset. Smaller pumps have just become available early in 1984. Starting CSII (the Autosyringe AS6C) with these children would have evoked images not of children with pumps but of pumps with children. Finally, one child started with CSII instead of the CT because of her family history. Her 2 year-older diabetic sister had just started with CSII, because of a brittle diabetes. Her well-being and metabolic control had improved considerably. Not only the risk of meeting the same problems with this second child, but especially in consideration of all the family had been through provoked the decision to start immediately with CSII. The data of these patients are not included in this thesis.

None of the participating children has any other relevant disease.

The mean age of the two groups differs significantly (CSII group: 9.5 $\pm$ 1.1 years; CT group: 7.0 $\pm$ 0.9 years), possibly as a consequence of the drop outs in the beginning of the study.

The two groups do not differ with respect to sex. Eight boys and 7 girls have started with CSII, whereas 7 boys and 8 girls have started with the CT.

As expected most children have either HLA-Dr 3, HLA-Dr 4 or HLA-Dr 3,4, except for only one child (20) who has HLA-Dr 1,8.

The two groups do not differ with respect to their socioeconomic background. Thus the only significant difference between the two groups of children is the age at onset.

Clinical onset of IDDM

At the onset no difference between the two groups has been found with respect to the degree of metabolic disregulation, endogenous insulin production, or duration of previous symptoms (polyuria, polydipsia, evident weight loss, listlessness). They are shown in table 5.II. Three children (14, 18, 30) have been hospitalized because of dehydration and/or metabolic disregulation requiring rapid intravenous administration of fluid and insulin. One conventionally treated child (16) has been hospitalized because of the absence of the nurse practitioner. As previously mentioned, in principle CSII treatment is started at the hospital. One exception has been made for a girl (8), who had a brother with IDDM. Since the family of this patient had sufficient knowledge of the disease itself, starting CSII at home (as only new element) seemed justified. (One of the drop outs - with a positive family history for IDDM - also started at home with CSII for the same reason).

Table 5.II The clinical onset of IDDM

CSII patients						CT patients					
patients	blood glucose (mmol/l)	pH[1]	keto-nuria[2]	duration of symptoms[3]	duration of admission[4]	patients	blood glucose (mmol/l)	pH[1]	keto-nuria[2]	duration of symptoms[3]	duration of admission[4]
1	23.5	0	1	2	3	16	22.9	0	1	2	2
2	14.9	0	1	4	2	17	15.3	0	1	3	0
3	22.2	0	1	1	3	18	60.0	1	1	1	3
4	17.0	0	1	3	2	19	40.0	0	1	2	0
5	19.2	0	1	2	2	20	19.8	0	1	1	0
6	12.0	0	0	3	3	21	30.3	0	1	0	0
7	27.2	0	0	1	1	22	17.4	0	1	0	0
8	14.9	0	0	0	0	23	31.0	0	1	0	0
9	18.6	0	0	2	2	24	12.5	0	1	1	0
10	18.1	0	1	2	1	25	19.2	0	1	1	0
11	17.8	0	1	1	2	26	18.2	0	1	0	0
12	8.0	0	1	2	2	27	27.0	0	1	2	0
13	23.1	0	1	0	2	28	13.3	0	0	0	0
14	45.4	0	1	0	2	29	33.8	0	1	0	0
15	21.5	0	1	1	1	30	45.6	0	1	1	3

1) pH $\geq$ 7.2 : 0
pH < 7.2 : 1

2) presence of ketonuria : 1
Absence of ketonuria : 0

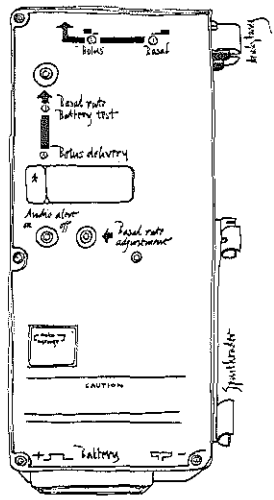
3) duration of symptoms before the onset of IDDM
2 weeks : 0
2 - 4 weeks : 1
9 - 12 weeks : 2
13 - 20 weeks : 3
> 20 weeks : 4

4) duration of admission
no admission : 0
1 - 7 days : 1
8 - 14 days : 2
15 - 31 days : 3
> 31 days : 4

FEASIBILITY AND PSYCHOLOGICAL IMPACT OF CSII

Pump treatment is usually started during a hospitalization. Hospitalization is certainly necessary for the newly diagnosed children, participating in this study. So far two types of pumps are used: the Autosyringe AS6C and the Eli Lilly/CPI Betatron 9204. The pumps are shown in figure 5.1a and 5.1b. For more detailed information on the functioning of those pumps the reader is referred to the two instruction booklets.

During hospitalization the practical skills needed for an adequate use of the pump are learned by patients and/or parents. The filling of the syringe and the catheter without air bubbles, the insertion of the needle in subcutaneous tissue, the adjustment of a basal rate and administration of bolus doses are skills that have to be performed correctly before the patient is allowed to leave the hospital. Once every day a new battery (recharged) is to be put into the pump.



1a 1b

Figure 5.1a and 1b. The 2 pumps:

1a: Autosyringe AS6C
1b: Eli Lilly/CPI Betatron 9204

From the instruction booklets, designed by Berenice Noordam

In most cases the syringe is refilled once a day. The needle and catheter are changed every 2 to 7 days and in case of skin infiltration, obstruction or activities which can only be performed without pump (swimming). The place where the pump is carried during daily life, differs per patient. Some children wear it on their side (on a belt) just like the very popular walkman or in their pockets. Others carry it under their arm, in a small bag attached to shirt or bra. Only a few children wear the pump on their back or belly. Most mothers (and fathers) have proven quite inventive by making small pockets of cotton or corset tape on shirt or bra. These pockets can be closed with "sticking tape". In this way each child can choose its own preferred place.

One may wonder how much time the pump costs the children. One child told us, that he spent at most 10 minutes per day on it and compared it to brushing his teeth. Usually it will vary from 10-20 minutes (including a total change of the infusion system) to 5 minutes (only the change of the battery and the syringe).

Measuring blood glucose levels, ketonuria and glucosuria is also taught in the hospital.

The insulin dose is given as a basal rate (continuously during 24 hours) and as bolus before each meal. Short acting insulin is always used in the pump. In general, the basal rate consists of 40% to 60% of the total dose. In younger children this ratio changes towards 25% basal and 75% bolus doses. The boluses are usually equal for each meal, although differences in activities or in caloric intake during a meal may result in different requirements. Preferably bolus doses are given half an hour before each meal. In practice, however, this will only be done at breakfast. The bolus is given before showering and getting dressed. The basal rate is determined on the basis of fasting and early morning blood glucose levels (03.00 h). The latter are measured about once every month. Bolus doses depend on the blood glucose values before and after the meals.

Patients and/or parents are advised to control the blood glucose level 3 to 5 times a week. The same advice is given to the CT group. Blood glucose values between 4.4 and 10.0 mmol/l are pursued.

Newly diagnosed children and their parents receive the same information concerning the theoretical background of diabetes (see chapter 3). Generally the nurse practitioner will give this instruction, but sometimes the department nurses take over.

Adjustments in special situations (see table 3.I) can be accomplished by changes in the basal rate as well as in bolus doses. An advantage - especially for children - is the easy way in which extra insulin can be administered. However, if hyperglycaemia seemingly without explanation is found, the entire system (syringe, catheter with needle) must be replaced. Several sports (swimming, rugby) require extra action since they can not be done at all or less well with a pump. The pump must be disconnected and reconnected afterwards.

During the first period after diagnosis the timespan without pump - and as a result without insulin - can last surprisingly long (sometimes upto 6 hours) without causing metabolic disregulations. However, after several months (for some children several years !!) it becomes evident - through rising blood glucose levels - that extra insulin must be administered before or after the period of disconnection. The duration of this period without insulin has to be reduced in time to a maximum of one hour.

Acceptation of CSII

Opinions of parents and patients have been asked regularly by the doctor during the visits to the hospital and by the nurse practitioner. Especially during warm weather patients have hesitated and seriously considered changing the pump therapy into injections. Still, none of them really wanted to start with CT. After 28 months of CSII one child (4) has decided to stop the CSII treatment. So far the other children all want to continue. Thus far, the insurance companies of 5 of the children, who have finished the study, have agreed to take over the costs of pump therapy after the two years of the study.

Problems

A new therapy never before used in a certain population will be accompanied by new problems.

The problems encountered with CSII treatment in more than 360 patient months (considering only the participating CSII children) are listed in table 5.III.

The problems are divided in 3 groups: directly caused by failure of the pump (I), errors or negligence of the patient (or parents) (IIa), and topical reactions at the insertion place (IIb).

The frequency with which these problems have been reported during the first year is scored 1 (< 5 times), 2 ($\geqslant 5$ times, < 15 times) or 3 ($\geqslant 15$ times).

After a fall in the water by one of the children (the drop out, treated with CSII) her Autosyringe AS6C started to administer continuously increased insulin doses, obviously requiring an immediate removal of the pump. The fact that the pumps are not waterproof has been confirmed by other accidents. Accidently putting the pump in the washing machine or in the toilet has resulted in irreparable damage as well. To what extent these actions point to problems in handling the pump or problems with the acceptation of the disease remains questionable. Except for these problems the pumps have proven to be "child-proof".

TABLE 5.III Problems with CSII

Pump-related	Frequency*	Patient-related	Frequency*
I. Defective syringe holder	2	IIA Forgotten to give meal doses	3
Defective batteries	3 **	Forgotten to change/refill the syringe	2
Defective charger	1	Forgotten to change/charge the battery	2
Detachment of the needle from the catheter	1		
Defective syringe top	2	Too late change of the catheter and needle	2
Leakage of the syringe	2	Air bubbles in the catheter	2
Alarm without a clear explanation	1	Clogged catheter (blood clot)	2
		Detached catheter (from the skin)	2
Inadequate adding system	1		
		IIB Irritation of the skin at the insertion place (scratch effects)	2
		Infiltration around the insertion place	2
		Haematoma at the insertion place	3

* 1: < 5 times
2: < 15 times, ⩾ 5 times
3: ⩾ 15 times

** only during the first 6 months, because of a poor batch of batteries.

A serious problem has been caused by the detachment of the needle (inserted in the subcutaneous tissue of the abdomen) from the catheter. This necessitated surgical intervention, with local anaesthesia, to remove the needle. The adding system (of Eli Lilly/CPI Betatron 9204) has caused commotion twice by indicating entirely different doses from what was expected. The correct and planned dose of insulin was administered anyway and no metabolic disregulation occurred. It was possibly caused in one case by a defective back-up battery. In both cases the pumps have been returned to the producers in order to be checked over and repaired.

Defective syringe tops resulting in leakage between the syringe and the catheter and leaking infusion sets have evoked blood glucose increases, especially if the catheter is changed in the evening (and the deficit is not noticed until the next morning).

Defective syringe holders of the Autosyringe AS6C are seen rather often. This defect can be caused easily be inserting the syringe into the holder too brusquely (haste??).

The first batch of batteries, belonging to the Eli Lilly/CPI betatron 9204, had to be replaced because some of them did not function correctly for at least 24 hours.

The patient-related problems speak for themselves. Meal doses are certainly easily forgotten in the first period after the diagnosis, especially by teenagers at school before lunch. This error is usually corrected during or shortly after the meal.

Clogged catheters, usually caused by a blood clot, are frequently seen in youngsters after a romp with friends, brothers and sisters, and in older children after sports. Removal of the catheter is not always necessary. In case a meal dose has to be given the clot may be removed through this shortly after its discovery.

Air bubbles form a problem also known by syringe users. It is very important, however, that the syringe as well as the catheter are free of air bubbles, since air replaces insulin.

During the first period of pump use, the injection technique has been changed for several patients. To prevent leverage of the part of the needle still in the catheter (usually about 50%) the needle is bent just beyond the catheter. Thus for each patient an ideal angle can be obtained to administer the insulin deeply into the subcutaneous tissue. This has resulted in a reduction of the hematoma at the insertion site.

Infiltration around the insertion place has been considerably reduced by the use of Cremor Chlorhexidin FNA R. The application of a little bit of this cream on the skin before inserting the needle or after removal of the needle is very effective. If too much is applied before the needle is inserted, problems arise with the adhesive plaster, which will no longer stick.

Irritation of the skin caused by scratching has been reduced but not stopped by the application of Calmitol cream (5% calmitol in Cetomacrogolcream).

In general problems encountered with the use of pumps for children have been minor so far. They certainly do not form an obstacle for the continuation of this treatment in all age groups.

Required attention: phone calls and home visits

The last two parameters considered in evaluating the feasibility of CSII in newly diagnosed children are the frequency of phone calls and home visits. Their frequency has been assessed by checking the nurse practitioner's agenda and the patients' records.

Three arbitrary categories of telephone calls of patients/parents to the nurse practitioner can be distinguished:

1. seldom contact ($\leq$ 1 call per month)

2. regular contact (> 1 and ≤ 5 calls per month)
3. frequent contact (> 5 calls per month)

Frequent telephonic contacts have been made by the parents of 2 CT children. The parents of 8 CT and of 4 CSII children have regularly telephoned the nurse practitioner. The parents of 5 CT children and of 10 CSII children telephoned seldom. This suggests a distinct difference between the two groups with respect to the frequency of telephonic contacts.

About 245 visits to the homes of the patients have been made by the nurse practitioner. In 97 cases the purpose was initial education, metabolic regulation and practical lessons for the newly diagnosed CT children. These daily visits for instructional purposes have been made with a mean duration of 7.5 days. A refreshers' course (practical or theoretical) has been given 37 times to the CSII group and 59 times to the CT group. An interesting fact is the small annotation in the diary of the nurse next to the written appointment with the first CSII patient: "Must have a look how everything is going". She told afterwards that the purpose of her visit was for her own instruction to see how a child with CSII was doing at home!

Instruction to schoolteachers, general physicians etc. has been given 13 times for CSII children and 14 times for the CT group.

Home visits for psychological and/or pedagogical problems have been made 9 times for CSII children and 11 times for CT children. One CT child has not been visited by the nurse practitioner. Very good collaboration with district nurses has resulted in their involvement. During the first 3 months this child was visited daily by the district nurse (90 times!). Thereafter this frequency was reduced and now a check is made regularly (twice each month).

The frequency of home visits does not differ significantly. There is a light tendency for less visits to CSII patients. Of interest is, as yet unmentioned, the category of home visits not made for the benefit of the patients but by request of doctors with visiting colleagues. Several times parents and patients have been very kind in receiving these visiting foreign doctors at home, which is not always an easy matter considering inter alia the frequently occurring language barrier.

Psychological tests

So far, 15 of the 16 children who have finished the 2 years of follow-up have been tested psychologically. Of 1 CT child the parents have refused participation in psychological tests. Nine CT and 6 CSII children have been tested. The age (at the test moment) of the two groups differs significantly (CT group: 9.3 ± 1.2 years of age; CSII group: 14.9 ± 1.0 years of age).

The results of the tests are summarized in table 5.IV.

The two groups do not differ significantly with respect to the intelligence test or the Junior Dutch Personality Test. Compared with the scores for the Junior Dutch Personality Test of normal children, the CT group has normal scores for 3 items: perseverance, dominance and inadequacy. Their scores are low normal for the social inadequacy and recalcitrance. The score for dominance of the boys is low-normal and for the girls normal. The CSII group has normal scores for inadequacy, perseverance and social inadequacy. For recalcitrance the score is high. The two boys score in the normal range for dominance, whereas the girls score high on this scale.

In the Family Relation Test the possibility to express feelings towards a sibling has been excluded for children without siblings. The CSII children show significantly more negative feelings towards their mothers than the CT children. The feeling of overprotection by any person (siblings, parents or nobody) is not experienced more often in either one of the two groups.

The scores of the fathers and the mothers in the Family Environment Scale are all within the normal range. The mothers of the 2 groups score significantly different with respect to the control exerted by the family members towards each other. The mothers of the CSII group score significantly lower than the mothers of the CT group. The fathers' answers differ with respect to the item on family organization. The fathers of CSII children score significantly higher. The incongruence scores between fathers and mothers in both groups do not show a significant difference and are within the normal range.

The Diabetes Questionnaire results only in significantly different scores for the two groups with respect to the item concerning physical complaints. The CSII group indicates that it is less bothered by physical complaints.

Application of the test of Friedman reveals information on the comparability of the 5 observers in the Assessment of Acceptation Scale. Because 1 father has not participated at all and because by accident 1 question (on 1 child) has not been answered by one member of the diabetes team, the scores of 12 to 14 children are used in the test of Friedman ($\alpha < 0.05$). The 5 observers are comparable with respect to questions 2 and 4, but score differently for questions 1, 3 and 5. Since not all the children can be included in the combined score, the individual scores (for each observer) have been given in table 5.IV.

The scores on the first question by fathers, mothers and one team member indicate a significant difference between the acceptation of IDDM and coping with it by the CSII group versus the CT group. The CSII treated children are assumed to accept their diabetes better. Two of the team members maintain that acceptation by the two groups is similar. The combined score for the metabolic control does not reveal a significant difference contrary to the individual scores. However, one must take account of the fact that only 12 children are included (instead of 15). The physical condition of the CSII group is regarded as significantly better than that of the CT children by all observers except one (one of the diabetes team members). The compliance towards

Table 5.IV Psychological tests:

ⓐ - tests, answered by the children
ⓑ - tests, answered by parents of the participating children and diabetes team

ⓐ Tests	Number of Patients		Wilcoxon Mann & Whitney
	CSII group	CT group	P-value *
WISC-R WIPPSI	6	9	> 0.05
Junior-Dutch Personality Test	6	5	> 0.05
Family Relation Test	6	9	< 0.05 for 1 item: - feelings towards mothers
Diabetes Questionnaire	6	9	< 0.05 for 1 item: - physical complaints

ⓑ Tests	Number of Participants					Wilcoxon Mann & Whitney
	CSII group		CT group		Diabetes Team	P-value *
	Fathers (F)	Mothers (M)	Fathers (F)	Mothers (M)	(DT)	
Family Environment Scale	6	6	8	9	-	< 0.05 for - organization : F - control : M
Assessment of Acceptation Scale	6	6	8	9	3	< 0.05 for - acceptation : 1 F, M, 1 DT - metabolic control : 2 F, M, 3 DT - physical condition: 3 F, M, 2 DT - compliance : 4 F, 1 DT - psychical health : 5 F, 2 DT

* In case of significant differences, the relevant item is separately mentioned.

advice from the diabetes team is considered to be equal for both groups, analysing the combined scores. Individual scores, however, (of the fathers and one of the team members) show a significant difference between the two groups, indicating that advice from the diabetes team is executed more easily by the CSII group. The psychical health of the two groups is judged differently by the various observers. Two members of the diabetes team consider the psychical health of the CSII group to be significantly better. However, the fathers score in such a way that the opposite result is obtained. The mothers and one of the team members assess the psychical health alike in both groups.

METABOLIC CONTROL

sHbA1

To give a rough impression of the course of sHbA1 the mean sHbA1 values of the 2 groups are shown in figure 5.2.
More important, however, are the individual data, listed in table 5.V.

The sHbA1 percentages at onset do not differ significantly between the two groups.

The slope of the Mood lines varies in the CSII group between -0.1 to -0.3 (mean: +0.06). The Mood lines of the CT group show a slope of -0.2 to +0.1 (mean: +0.02). The 2 groups do not differ significantly with respect to this slope. In most children the sHbA1 levels remain rather constant during the first year (excluding the first 2 months).

The sHbA1 on the Mood line differs significantly between the 2 groups after 1 year, indicating a better overall metabolic control in the CSII group.

The variability indices do not differ significantly between the two groups (CSII group (range): 0.27 - 0.62; CT group (range): 0.27 - 0.72).

The moment at which the sHbA1 level exceeds 9.0% is significantly earlier in the CT group compared with the CSII group (CT group: 3.7 $\pm$ 0.8 months, range: 2-11 months; CSII group: 11.1 $\pm$ 2.5 months, range: 2-26 months) *.
Four children, treated with CSII, have a sHbA1 still in the normal range 1 year after onset, whereas all the CT children have higher sHbA1 percentages.

* For these results all data thus far obtained, are used. For those children still having UCP above 30%, a normal sHbA1 and an insulin dose below 0.5 U/kg/24h, a maximal score (2 years) is used for the calculations. The mean values given are lower than they are in reality. Two CSII and 2 CT children have a UCP above 30% after 2 years of diabetes. One CSII treated child has an insulin dose below the limit of 0.5 U/kg/24h. Finally 4 CSII children still have a sHbA1 in the normal range after 2 years of follow-up.

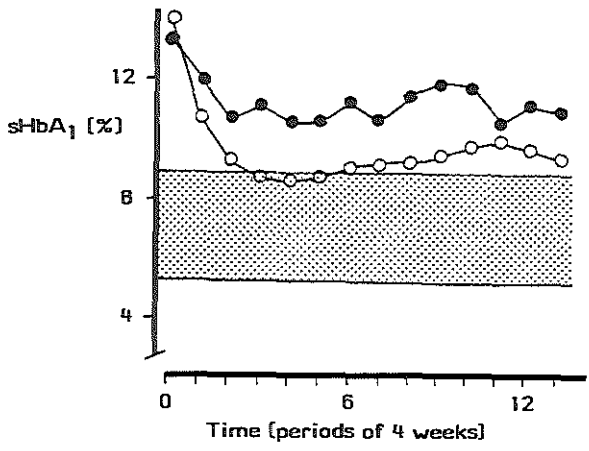


Figure 5.2. Comparison between the sHbA1 (%) in diabetic children treated with CSII (0-0) and CT (●-●). The shaded area represents the range for healthy children (n = 42, age: 1 - 20 years).

TABLE 5.V Characteristics of sHbA1

CSII patients					CT patients			
patients	initial sHbA1 (%)	sHbA1 (t=1 yr on Mood line) (%)	end of * remission (months)		patients	initial sHbA1 (%)	sHbA1 (t=1 yr on Mood line) (%)	end of * remission (months)
1	16.8	6.9	**		16	10.4	9.6	2
2	12.3	11.7	7		17	11.1	12.9	2
3	14.4	7.5	**		18	19.7	12.6	5
4	18.3	12.9	2		19	18.0	9.6	11
5	11.7	8.7	13		20	13.3	12.3	2
6	13.2	6.6	**		21	11.4	14.7	2
7	16.1	11.4	6		22	14.6	10.8	2
8	9.0	12.0	2		23	9.0	10.8	9
9	10.0	9.0	6		24	12.5	9.9	2
10	16.6	8.1	2		25	13.1	9.0	2
11	17.6	9.0	5		26	12.1	11.1	2
12	11.4	8.7	**		27	16.0	9.9	8
13	14.4	9.9	8		28	9.0	11.4	3
14	14.7	8.7	2		29	15.4	12.6	2
15	13.9	10.8	9		30	13.8	12.6	2

* the end of remission with respect to sHbA1 (sHbA1 > 9.0%)
** the sHbA1 is still $\leq$ 9.0%

Home measured blood glucose levels

The diaries demonstrate an enormous variety in frequency and time of and reasons for the determination of home measured blood glucose values. Diaries have not been obtained from 3 children. This does not imply that measurements have not been performed. The booklets may have been gotten lost either in the hospital or at home. Sometimes small papers are used in the absence of a diary, which are doomed to disappear. From all but 3 children (all CT children) a mean frequency of blood glucose measurements has been calculated to get an impression of this frequency in the two groups. In the pump group a mean of 21 determinations (range: 9-42) per 28 days is found. In the CT group this number is 20 (range: 10-27) per 28 days. Although this result is only based on a part of the groups, it suggests that blood glucose monitoring is performed with a similar frequency in both groups.

From the insurance companies the following information has been obtained concerning test strips. Six insurance companies have not replied. Nine companies could not reveal which materials had been declared and/or refunded. Fifteen companies, insuring 8 CSII and 7 CT children, could indicate how many blood test strips had been refunded. A mean of 6.4 pots of Hemoglucotest strips has been refunded to the CSII group, whereas a mean of 9.6 has been refunded to the CT group during the first year. The difference is significant. One has to be careful with conclusions since only information on a part of the groups has been obtained. One may assume that the data missing are aselectively distributed over the 2 groups. Thus, calculation of the noted home measured blood glucose values suggests a similar frequency for both groups, whereas a larger amount of pots is declared by the CT group.

Hypoglycaemia requiring glucagon administration intramuscularly has occurred once in both groups. In the pump group a child (3) got a hypoglycaemia in the first month after onset. The meal dosis before breakfast had been administered, just as in the hospital, one half hour before breakfast. Without the stress of the hospital and with the increased endogenous insulin production, this timespan proved to be too long and a hypoglycaemia occurred. The hypoglycaemia of the CT child is less easily explained. It concerns a young child (16) with poor injection sites, probably resulting in less regular insulin uptake. This in combination with the unpredictability of childrens' activities may have evoked this hypoglycaemia.

As far as the less severe hypoglycaemic periods are concerned, incomplete information has been obtained from diaries. The patients' records also provide information on whether or not hypoglycaemic periods have occurred, but do not report the frequency of the hypoglycaemic periods per month.

The diaries have been used to calculate the mean frequency of hypoglycaemic periods per 28 days. Again information from 3 CT children is missing. A mean frequency of 0.8 hypoglycaemic periods per 28 days (per child) was found in the 15 children treated with CSII (range: 0 - 2.2) and 2.3 periods per 28 days (per

child) in the 12 CT children (range 0 - 14.0). This difference is not significant. The patients' records reveal that during the hospital visits 3.9 times per month (range: 2-8) hypoglycaemic periods have been reported by the CSII group vs 5.2 times per month (range: 1-8) by the CT group. This difference is also not significant.

Hospitalization

During the first year one CT child (21) has been hospitalized as well as one (14) of the CSII treated children. For the latter the reason for hospitalization was an isotone dehydration because of severe gastroenteritis (without at that moment a ketoacidosis). The CT patient was hospitalized because of very poor metabolic regulation.

Intermediary metabolites

Of the intermediary metabolites only the branched chain amino acids have been determined in all patients. The mean values (given as mean ± 1 SEM) for the CSII and the CT group are respectively after 6 months for leucine 0.19 ± 0.02 and 0.17 ± 0.02 mmol/l; for isoleucine 0.10 ± 0.01 mmol/l and 0.09 ± 0.01 mmol/l and finally for valine 0.32 ± 0.03 mmol/l and 0.31 ± 0.03 mmol/l. After one year mean values are found respectively for leucine 0.20 ± 0.02 mmol/l and 0.19 ± 0.01 mmol/l, for isoleucine in both groups 0.10 ± 0.01 mmol/l and for valine 0.32 ± 0.02 mmol/l. It is evident that these concentrations do not show a significant difference. They are, however, slightly increased when compared to reference intervals.

Pyruvate, lactate, 3-OH-butyrate, triglycerides and free fatty acids ought to be determined each time the patients come to the Diabetes Clinic for the glucagon stimulation test after an overnight fast. In the initial period of the study, however, several practical problems concerning the method of blood sampling have made determinations difficult. This has resulted in a reduced number of tested patients. The data are given in table 5.VI. The results of the tested patients do not differ significantly with respect to each other.

HDL-cholesterol and cholesterol

The cholesterol levels of the two groups do not differ significantly after 6 months nor after 1 year (CSII group: after 6 months: 4.6 ± 0.3 mmol/l; after 1 year: 4.9 ± 0.4 mmol/l; CT group: after 6 months: 5.1 ± 0.2 mmol/l; after 1 year: 4.6 ± 0.2 mmol/l). The difference in each group in time is not significant either. The individual values for both groups are in the normal range except for one patient (7). He has a mild hypercholesterolaemia with a mean level (in the first 6 months) of 7.6 mmol/l and in the second part of the year of 8.7 mmol/l. Further investigation revealed a positive family history (of the father's side) for early cardiovascular problems. This also points towards

Table 5.VI Intermediary metabolites

CSII patients

Time after onset (years)	lactate (mmol/l) ½	lactate (mmol/l) 1	pyruvate (μmol/l) ½	pyruvate (μmol/l) 1	3-OH-butyrate (mmol/l) ½	3-OH-butyrate (mmol/l) 1	TG (mmol/l) ½	TG (mmol/l) 1	NEFA (mmol/l) ½	NEFA (mmol/l) 1
Patients										
1	1.26	1.43	54	67	0	0.1	0.44	0.28	0.53	0.82
2	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-
4	-	1.17	-	58	-	0.1	-	0.68	-	0.52
5	-	-	-	-	-	-	-	-	-	-
6	-	1.02	-	72	-	0.5	-	-	-	-
7	1.47	1.08	33	61	0.1	1.0	0.75	0.80	0.19	1.38
8	1.10	1.11	25	22	0.1	0.1	0.38	0.55	0.46	0.66
9	1.24	-	87	-	0.4	-	0.84	0.53	1.66	1.36
10	1.60	1.45	66	14	0.6	0.4	0.53	0.69	1.22	1.06
11	1.76	1.86	80	54	0.1	0.1	0.40	0.78	0.59	0.57
12	1.23	3.03	56	61	0.1	0	0.63	0.90	0.50	-
13	-	2.60	26	59	0.3	0.4	0.75	1.28	1.14	0.85
14	-	1.37	-	50	-	0.3	-	0.66	-	-
15	0.61	1.42	42	67	0.2	0.3	0.58	0.36	0.62	-

CT patients

Patients	lactate (mmol/l) ½	lactate (mmol/l) 1	pyruvate (μmol/l) ½	pyruvate (μmol/l) 1	3-OH-butyrate (mmol/l) ½	3-OH-butyrate (mmol/l) 1	TG (mmol/l) ½	TG (mmol/l) 1	NEFA (mmol/l) ½	NEFA (mmol/l) 1
Patients										
16	-	-	-	-	-	-	-	-	-	-
17	-	-	-	-	-	-	-	-	-	-
18	-	-	-	-	-	-	-	-	-	-
19	-	-	-	-	-	-	-	-	-	-
20	-	1.50	-	61	-	4.3	-	0.52	-	0.71
21	-	2.00	-	13	-	0.6	-	0.78	-	0.90
22	2.37	0.95	125	28	0.3	0.1	0.59	0.34	0.90	0.98
23	0.83	1.56	70	40	0.2	2.2	1.85	0.87	0.89	2.29
24	1.00	1.79	79	56	0.2	0.3	0.41	0.51	0.81	0.07
25	1.25	1.80	58	61	0.1	0.3	0.95	0.41	0.92	0.86
26	-	-	-	-	-	-	-	-	-	-
27	1.61	0.96	44	53	0.2	0.3	0.88	0.63	1.50	0.54
28	1.92	1.52	43	63	0.3	0.4	0.64	0.37	-	1.31
29	1.41	1.34	76	29	0	0.3	0.75	0.58	1.18	1.09
30	2.26	1.76	89	76	3.5	0.8	0.71	0.82	1.70	0.94

hypercholesterolaemia. Extra dietary advice has been given in order to reduce the cholesterol intake as much as possible.

The mean HDL cholesterol values are for both groups in the normal range (CSII group after 6 months: 1.28 ± 0.04 mmol/l; after 1 year: 1.39 ± 0.07 mmol/l; CT group: after 6 months: 1.58 ± 0.09 mmol/l; after 1 year: 1.49 ± 0.06 mmol/l).

After 6 months the CSII group has a significantly lower HDL cholesterol level compared with the CT group. However, after one year this difference has disappeared. One patient (2) has a mean HDL cholesterol level just below the lower limit (0.61 mmol/l). Since, except for 1 value, the concentrations are within the reference interval no further action has been undertaken.

Physical development

All children are growing above the 10th percentile (weight for height). Five of the CSII and 3 of the CT children are growing above the 90th percentile, weight for height, but they also followed this percentile before the overt onset of the disease.

The exogenous insulin administration

The insulin doses administered after 6 months and 1 year do not differ significantly between the 2 groups (respectively 0.50 vs 0.48 U/kg bodyweight/24h and 0.71 vs 0.66 U/kg bodyweight/24h for the CSII and the CT group). The increase in the CSII group after the initiation of the treatment is 0.35 U/kg bodyweight/24h (from 0.36 in the first month towards 0.71 U/kg bodyweight/24h after 1 year). In the CT group a larger dose is given in the first month (0.44 U/kg bodyweight/24h) resulting in the relatively low increase of 0.22 U/kg bodyweight/24h during the first year. The insulin dose has been changed in total 63 times in the CSII group resulting in a mean of 0.15 U/kg bodyweight/24h at one time and 74 times in the CT group with a mean of 0.12 U/kg bodyweight/24 h at one time.

The moment at which the insulin dose exceeds the 0.5 U/kg bodyweight/24h varies in both groups from 1 to 26 months with a mean in the CSII treated group of 9.1 ± 2.1 months and in the CT group of 9.5 ± 1.7 months, thus not indicating a significant difference between the two groups.

In short, the metabolic control differs significantly between the 2 groups with respect to the sHbA1. Intermediary metabolites and hypoglycaemic periods do not differ significantly. Home measured blood glucose testing has been performed probably about as often in both groups. Incomplete information prevents although definite conclusions. The insulin dose does not differ significantly between the two groups after 6 months and 1 year. The moment at which the insulin dose exceeds the 0.5 U/kg bodyweight/24 h does not differ significantly between the 2 groups.

ENDOGENOUS INSULIN RESERVE

Urinary C-peptide excretion

The course of UCP, expressed as mean value for each group, is shown in figure 5.2.

More important is the evaluation of the individual data. The course of UCP shows in most cases a spiking pattern. The variability indices vary considerably in both groups (CSII group (range): 0 - 0.77; CT group (range): 0 - 0.66). No significant difference between the two groups is noted regarding the variation.

Since endogenous insulin production is one of the three criteria for the remission period, it is necessary to define precisely what the end of the remission period is with respect to the UCP. What is really the point of no return regarding the UCP? An investigation of the results of the individual subjects (including all data) thus far obtained suggests that 3 successive UCP of 30% or less (of the predicted mean for a specific age) will not be followed by a spike above 30% but rather by a final decrease. Therefore, the first time there are three successive values of UCP of 30% or lower, this point in time is used to indicate the end of the remission with respect to the endogenous insulin reserve. The characteristics of the UCP course are depicted in table 5.VII.

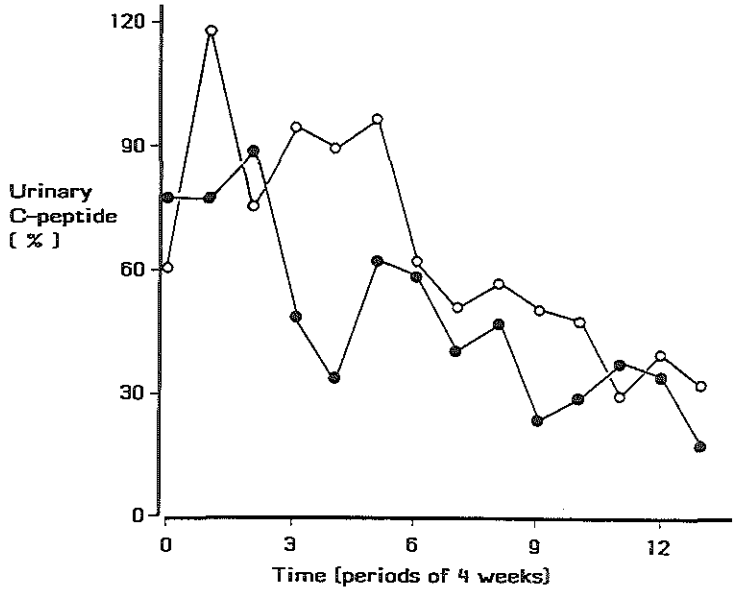


Figure 5.2. Comparison between the urinary C-peptide excretion (expressed as percentage) in diabetic children treated with CSII (0-0) and CT (●-●)

Table 5.VII Characteristics of urinary C-peptide excretion (expressed as percentage)

CSII patients							CT patients						
Patients	Initial UCP (%)	End peak (months)	Max UCP (%)	Predicted time UCP = 0 (months)	End of remission (months)		Patients	Initial UCP (%)	End peak (months)	Max UCP (%)	Predicted time UCP = 0 (months)	End of remission (months)
1	41	-	91	**	> 26		16	76	-	80	12.6	8
2	247	9	333	**	> 26		17	83	10	314	27.2	11
3	13	7	238	57.8	> 26		18	*	-	114	16.4	22
4	7	8	231	21.4	11		19	79	-	140	55.6	14
5	24	-	117	19	8		20	15	-	45	38.8	4
6	109	8	155	93.4	> 26		21	49	-	60	28	6
7	35	8	117	13	7		22	52	-	56	21.4	9
8	180	8	180	13.6	7		23	179	7	179	34.2	22
9	91	8	210	19.8	7		24	100	-	177	23.8	> 26
10	30	-	67	37.6	12		25	141	-	141	24.2	22
11	8	-	67	15.8	8		26	91	5	186	28	5
12	58	-	105	**	> 26		27	77	-	83	33	> 26
13	19	-	93	17.8	12		28	78	-	90	22.4	14
14	45	-	161	44.4	16		29	20	-	23	13.6	0
15	28	-	51	26	11		30	43	-	43	4	2

* No UCP has been determined

** UCP negativety could not be determined because of:
- positive slope
- long lasting peak
- insufficient values

The initial UCP does not differ significantly between the 2 groups.

After the start of the treatments an increase of UCP - labeled according to previously mentioned criteria as peak - is observed significantly more often in the CSII group (7 vs 3 times). The duration of these peaks does not differ between the 2 groups.

The decline of UCP in time reflected by the slope of the line, is significantly less steep in the CSII group. In 2 children with pump therapy no slope could be calculated because of insufficient samplings after the peak to fit a line. In 1 CSII patient no decline but even an increase is observed during the first year. Whether this will continue during the second year remains to be seen.

The maximal UCP does not differ significantly between the 2 groups. Prediction of the point of time at which no UCP can be elucidated anymore (obtained through extrapolation of the Mood line) can not be made in the case of 3 CSII patients, either because of the increase of the Mood line or because of the impossibility to draw a line. No significant difference is found between the two groups with respect to this point in time.

The decrease of UCP below the critical level ($\leq$ 30%) is found after 15.3 $\pm$ 2.1. months (range: 7->26 months*) in the CSII group and after 12.7 $\pm$ 2.3 months (range: 0->26 months*) in the CT group. These points of time do not differ significantly between the two groups.

A significant correlation is found between the initial UCP values and those (not on the line) after 1 year. This relationship is found as well for all children as for the 2 groups separately. (All children: $r = 0.55$, $p < 0.05$; CSII group: $r = 0.80$, $p < 0.05$; CT group: $r = 0.67$, $p < 0.05$).

Glucagon tests

The glucagon stimulation test has been performed in 23 children (13 CSII and 10 CT children) after 6 months and in 27 children (13 CSII and 14 CT children) after 1 year. Most of the children who have not been tested after 6 months (12, 14, 16, 17, 21, 26, 30) belong to the younger ones. In three of them (12, 14 and 30) insertion of the intravenous catheter has failed.

* For these results all data, obtained thus far, are used. For those children still having UCP above 30%, a normal sHbA1 and an insulin dose below 0.5 U/kg /24 h bodyweight a maximal score (2 years) is used for the calculations. The mean values given are lower than they are in reality. Two CSII and 2 CT children have a UCP above 30% after 2 years of diabetes. One CSII treated child has an insulin dose below the limit of 0.5 U/kg bodyweight/24 h. Finally 4 CSII children still have a sHbA1 in the normal range after 2 years of follow-up.

At the beginning of this study, frequent execution of glucagon stimulation tests in very young children has not been considered acceptable. Hence, the frequency was reduced to twice during the entire study. The reduction of complaints during the stimulation test because of slow intravenous administration has changed our attitude and except for the first group of toddlers, youngsters also have been tested 4 times. One CT child has not been tested after 6 months because the appointment was mistakenly made too early (2 months after the onset). The difference in time is too great to include these results. After 1 year, 1 CSII child (3) has refused to participate in the test because of complaints he had during the previous test. For one child (14) the quantity of blood sampled was insufficient for the determinations. Finally, for one child (24) the insertion of the intravenous catheter failed. Thus, the results of the tests given in table 5.VIII must be interpreted with care.

Table 5.VIII Plasma C-peptide values before and after stimulation with 1 mg glucagon

	time (months)	CSII group	n	CT group	n
Fasting plasma C-peptide levels (nmol/l)	6	0.22 ± 0.08	13	0,18 ± 0.04	10
	12	0.13 ± 0.03	14	0.12 ± 0.03	14
Peak value of plasma C-peptide after glucagon stimulation (nmol/l)	6	0.33 ± 0.04	13	0.38 ± 0.06	10
	12	0.25 ± 0.05	13	0.20 ± 0.05	14
Plasma C-peptide values during glucagon stimulation (AUC)	6	14.1 ± 2.1	13	14.5 ± 2.5	10
	12	10.7 ± 2.0	13	8.1 ± 1.6	14
Mean plasma C-peptide values during glucagon stimulation (nmol/l)	6	0.24 ± 0.03	13	0.25 ± 0.04	10
	12	0.18 ± 0.03	13	0.13 ± 0.03	14

Although the CSII group has slightly higher plasma C-peptide levels after 1 year this difference is not significant.

In summary, the UCP course shows significantly more often a peak in the CSII group. Its path, as reflected by the slope of the Mood line, is also less steep in the CSII group. The variability does not differ significantly between the 2 groups. The initial, nor the maximal UCP or the levels after 1 year differ significantly between the 2 groups. The time at which no UCP is expected anymore (by extrapolation of the Mood line) and the end of the remission period (UCP $\leq$ 30%) are not significantly different for the 2 groups. The glucagon stimulation test shows no significant differences between the groups. It must be stressed, however, that not all the children have been tested.

IMMUNOLOGICAL PARAMETERS

At the onset of IDDM ICCA are detected in 60% (9 out of 15) of the CSII group and 67% (10 out of 15) of the CT group. ICCA-CF is found in 46% (7 out of 15) of the CSII group and 40% (6 out of 15) of the CT group. In 42% of the CT group and 46% of CSII (6 out of 14 in the CT group and 6 out of 13 in the CSII group) ICSA are detected. Of 3 patients ICSA has not yet been determined at 3 different intervals because of practical problems (patients 1, 6 and 20).

The data concerning the islet cell antibodies are given in table 5.IX.

Table 5.IX The immunological parameters

	CSII patients										CT patients									
	ICCA			ICCA-CF			ICSA				ICCA			ICCA-CF			ICSA			
Time after onset (years)	0	½	1	0	½	1	0	½	1		0	½	1	0	½	1	0	½	1	
Patients										Patients										
1	0	0	0	0	0	0	-	0	-	16	2	2	0	0	0	0	0	0	3	
2	3	3	3	3	2	2	0	0	0	17	2	1	0	0	1	0	0	0	2	
3	0	0	0	0	0	0	0	0	0	18	3	2	1	2	2	1	0	0	0	
4	2	4	4	2	3	3	2	2	1	19	0	2	0	0	2	0	0	0	0	
5	3	3	1	4	3	2	3	3	3	20	2	4	4	2	2	2	-	0	-	
6	0	2	0	0	2	0	-	0	-	21	2	2	2	0	2	1	3	2	1	
7	0	0	0	0	0	0	3	3	3	22	4	3	4	3	3	3	0	2	1	
8	2	0	0	2	0	0	0	0	0	23	0	0	0	0	0	0	0	2	0	
9	2	3	3	2	3	3	3	1	2	24	0	0	2	0	0	0	4	3	3	
10	2	2	2	0	0	2	0	0	0	25	0	1	0	0	0	0	3	0	2	
11	4	4	3	2	2	2	0	0	0	26	4	4	3	3	2	2	2	1	3	
12	3	3	2	0	2	0	1	0	1	27	3	2	3	2	2	2	3	0	0	
13	0	0	0	0	0	0	0	2	0	28	2	3	0	0	2	0	0	2	0	
14	4	1	2	4	0	0	0	0	0	29	4	4	4	4	3	3	1	2	2	
15	0	3	2	0	2	2	1	0	0	30	0	0	0	0	0	0	0	0	0	

No significant differences are found between the two groups with respect to these antibodies.

IgGIa levels do not differ significantly between the two groups at any point of time. They are given in table 5.X.

Table 5.X Insulin antibody production

time (weeks)	CSII patients IgGIa (U/l) *	CT patients IgGIa (U/l) *
0	0	0
12	0.064 ± 0.025	0.045 ± 0.022
24	0.178 ± 0.086	0.194 ± 0.123
36	0.137 ± 0.045	0.384 ± 0.232
48	0.131 ± 0.040	0.470 ± 0.297

* Determined by the method of Christiansen

One CT child (20) has an exceptional IgGIa production (3.95 U/l) explaining the large SEM. She is also the only child without HLA Dr 3 and/or HLA Dr 4.

At onset no insulin antibodies (IgGIa) were detected by the method of Christiansen, whereas with the more sensitive method in 5 of 15 CT children (33%) and in 4 of 13 CSII children (31%) insulin antibodies were found. The percentage bound insulin antibodies varies in the CT group between 0.3 and 2.8% and in the CSII group between 0.3 and 0.9%.

In summary, the 2 groups do not differ with respect to the presence of the immunological factors studied.

REMISSION PERIOD

If the 3 parameters - insulin dose (<0.5 U/kg/24h), UCP (≤30%) and sHbA1 (>9.0%) - are taken into account to calculate the duration of the remission, a significant difference is found between the two groups regarding the duration of the remission phase. The remission period in the CSII group lasts significantly longer than in the CT group (7.5 ± 2.0 versus 3.3 ± 1.5 months respectively). After one year, 3 of the CSII treated children (20%) and none of the CT children (0%) are still in remission. No remission is seen in 16 children (11 of the CT group and 5 of the CSII group).

In search of factors, possibly influencing the remission period , the relationship between several factors and the remission period has been analysed.

Characteristics of the patients

In this group of patients the duration of the remission period shows no relation with the age of the children. Although the boys show a slightly longer remission period (5.5 ± 1.5 months in the boys; 4.7 ± 1.8 months in the girls), this difference is not significant.

The HLA Dr types (HLA Dr 3,x; HLA Dr 4,x; HLA Dr 3,4) do not differ with respect to the duration of the remission period. One girl with HLA Dr 1,8 had no remission at all.

The socioeconomic background of the children does not seem to play a role either as is suggested by the not significant differences between the socioeconomic classes.

The 3 children who needed an intravenous administration of fluids and insulin show no remission period. The insulin doses of these 3 children exceed 0.5 U/kg bodyweight/24h from the first month onwards. The UCP of one of these children decreases rapidly below the limit of 30%. In the other 2, this limit has been passed at 11 and 16 months.

Presence or absence of ketonuria at onset does not result in a significantly different duration of the remission period (pH < 7.2 (n=1): no remission;ketones: positive but pH ⩾ 7,2 (n=24), mean duration of the remission: 5.2 ± 1.4 months; ketones negative (n=5): 6.0 ± 2.3 months).

Finally, no relationship is noted between the duration of the remission period and the duration of the symptoms before the overt onset of the disease.

Immunological factors

A clear relationship between the remission period and any of the determined immunological parameters has not been detected. Neither their presence at onset nor their course reveal any indication of a direct influence by them on remission.

The individual parameters

The Pearson contingency coefficient has been calculated for the individual values of sHbA1 and UCP in order to obtain information on a possible constant relationship between the metabolic control and endogenous insulin reserve. This results in distinct coefficients, varying from 0.0 to 0.51. Thus no fixed association exists between the sHbA1 and UCP.

The 4 children with a sHbA1 still in the normal range after 2 years all have a UCP above the lower limit (in total 7 children have a UCP above 30% after two years of overt diabetes). Only in 1 child the decrease in UCP below 30% precedes the increase in sHbA1. In the other children an increase in sHbA1 above 9.0% is observed before the decrease in UCP. It is evident that the glycaemic control is not the only important factor. Nevertheless its influence can certainly not be excluded.

The relationship between insulin doses and endogenous insulin reserve has not been calculated through the Pearson contingency

coefficient, because the insulin dose is often constant for several months. A possible correlation has been sought by calculating the Spearman coefficient of correlation for the insulin dose (at 6 months and 1 year) and the UCP (at 6 months and 1 year). For UCP the points on the Mood line have been taken, since they are influenced by all values.

A significantly negative correlation is detected at both points in time and in both groups (6 months: all children, n =28, r = - 0,68; CSII group, n=13, r = - 0,72; CT group, n = 15 ; r = - 0,52; 1 year: all children, n = 28, r = - 0,59; CSII group, n = 13, r = - 0,76; CT group, n = 15, r = - 0,57 ($p < 0.05$)). The differences between the correlation coefficients of the CT and the CSII group are not significant.

Analysis of the data, looking for a possible relationship between age, HLA types and antibody formation (either against the islet cell or against insulin), does not reveal a relationship. The presence of ICCA, ICCA-CF, ICSA and IgGIa nor their course show a relationship with the sHbA1, insulin dose or UCP. The presence of IgGIb, however, shows a significant negative correlation with UCP (on the Mood line) after 1 year. The patients with detectable IgGIb at onset have a significantly lower UCP after 1 year (IgGIb positive patients UCP: 10.4 $\pm$ 5.5%, IgGIb negative patients UCP: 32.1 $\pm$ 4.5%). They also reach, significantly earlier, the point of no return (UCP $\leq$ 30%) (IgGIb positive group: 2.7 $\pm$ 0.7 months; IgGIb negative group: 5.8 $\pm$ 1.4 months). Thus detectable IgGIb at onset is associated with a faster decrease of UCP. At onset patients with and without IgGIb do not differ significantly with respect to UCP (IgGIb positive group: 60.1 $\pm$ 24.4%; IgGIb negative group: 79.0 $\pm$ 12.0%).

Summarizing, although no fixed relationship can be demonstrated between UCP and sHbA1, a possible role of a normal metabolic control on the residual beta cell function can not be excluded. The insulin dose shows a linear relationship with UCP. This relationship seems to be more obviously present in the CSII group. Of the other parameters, only the presence of IgGIb at onset (negatively) influences the residual beta cell function.

SUMMARY

Pump therapy, started from diagnosis onwards in newly diagnosed diabetic children is very well feasible. The remission period lasts about 4 months longer in CSII patients. The glycaemic control is significantly better in the CSII group with respect to sHbA1 values.

A significant relationship is found in both groups between UCP and insulin doses after 6 and 12 months. UCP at onset shows a significant correlation with UCP after 1 year.

The presence of insulin antibodies (IgGb) before the start of insulin therapy shows a significantly negative association with the endogenous insulin production.

Further this summary serves to answer questions, raised in the previous chapter.

1. CSII treatment is feasible in previously randomized newly diagnosed children.
   - Four children "dropped out": 2 because of their age (≤ 5 years) and the pumps available at that time ; 1 because of her social background and 1 because of her family history.
   - The patients nor the parents require more attention as is reflected by phone calls and home visits from a nurse practitioner (rather the contrary).
   - The treatment and its consequences have been remarkably well accepted up to now by most patients and parents. One child (adolescent girl) has expressed the wish to stop the treatment and has done so. The other children want to continue the treatment, even after the end of the study period.
   - The problems occurring during CSII therapy are mild and do not necessitate termination of this therapy.
   - It is not yet possible to answer the question whether CSII reduces any possible negative effects of IDDM on the psychological functioning of the child since the data are incomplete. A marked difference is found between the 2 groups with respect to their physical complaints (much higher frequency in CT children). As for the social activities and contacts, the 2 groups do not differ significantly. This suggests that CSII does not form an impediment for children in their social life.

2. The children, treated with CSII achieve a significantly better metabolic control with respect to sHbA1.
   - Four of the CSII children continue (after 2 years) to have a sHbA1 percentage in the normal range, whereas after 11 months none of the CT children has a sHbA1 in the normal range. The variability index does not differ between the 2 groups. Neither intermediary metabolites nor cholesterol and HDL Cholesterol (after 1 year) differ significantly between the two groups.
   - The numbers of blood glucose measurements provided by the diaries of the children (incomplete) suggest a similar frequency in the two groups. According to the information (also incomplete) obtained from the insurance companies, the frequency of blood glucose measurements seems to differ significantly.
   - The insulin dose of the 2 groups does not differ significantly. The moment at which the critical level of 0.5 U/kg /24 h is exceeded, does not differ significantly either.

3. CSII therapy results in a significant - however temporary - prolongation of the remission period of about 4 months.
   - Although the endogenous insulin production (UCP) is higher most of the time in the CSII group, this difference is not significant. A peak in UCP is observed significantly more

often in the CSII group, together with a less steep decrease.
Neither initial nor maximal values differ significantly between the 2 groups, nor does the moment at which the critical level (UCP $\leq$ 30%) is passed.

- A significant correlation is found between the initial UCP and the UCP after 1 year. Although the correlation coefficients of the 2 groups differ considerably, this difference is not significant. The data of the glucagon stimulation tests (although incomplete) suggest the same: although the CSII group has slightly higher values, this difference is not significant.
- No fixed association has been found between sHbA1 and UCP. The existence of a critical level of sHbA1 can not be excluded, since only for one child a period was found with a sHbA1 in the normal range and the UCP below 30%. (Most children demonstrate first an increase in sHbA1 and subsequently a decrease of UCP). From these data, however, no definite conclusions can be drawn.
- The insulin doses show a significant relationship with UCP (after 6 months and 1 year). Although this association seems more outspokenly present in the CSII group, the difference between the 2 coefficients is not significant.
- None of the characteristics of the patients shows a relationship with the remission period and/or its individual parameters.
- Neither the presence nor the course of islet cell antibodies reveal a relationship with the remission period and/or its individual parameters.
- A significant negative association is found between the presence of insulin antibodies (IgGIb) at onset and UCP after 1 year. The presence of these antibodies is also associated with a significantly faster decrease in UCP levels.
- No difference is found in insulin antibody production (IgGIa) of the two groups. An extraordinary concentration (up to 3.95 U/l) is found in a CT girl with a particular HLA-Dr type: HLA-Dr 1,8. Antibody production certainly occurs in spite of treatment with human insulin, suggesting that other factors are important besides the purity of the insulin.

CHAPTER 6

EVALUATION AND RECOMMENDATIONS

FEASIBILITY AND PSYCHOLOGICAL IMPACT OF CSII IN NEWLY DIAGNOSED DIABETIC CHILDREN

Feasibility

The findings of this study suggest that CSII therapy is feasible in not selected newly diagnosed diabetic children (age: 1 - 16 years) who were consecutively referred to the SKZ. The presence of patient (and parent) education, self-monitoring, 24 hours telephone service and, last but not least, a home visiting nurse practitioner are necessary conditions for the execution of this prospective randomized study in children.

The feasibility of CSII therapy has been evaluated by taking the following factors into account:

- the acceptation of CSII by patient and parents
- the problems, encountered with CSII therapy (patient- or pump-related) and possible consequent metabolic disregulations (severe hypoglycaemia or ketoacidosis, requiring hospitalization)
- the time cost (frequency of phone calls to and home visits by the nurse practitioner)

Regarding the acceptation of CSII, our results are consistent with some and inconsistent with other studies (Van Ballegooie 1984, Becker 1984, Bougnères 1984, Schiffrin 1984). Of our 15 CSII patients only one, an adolescent girl, has stopped CSII therapy after 28 months. Becker obtained an entirely different result. In order to evaluate the long-term efficacy of CSII, 16 adolescents (age: 14 - 19 years, duration of IDDM: 3.75 - 14.5 years) started with CSII therapy. Twelve stopped with CSII from 2 weeks to 2 years after onset and 1 patient has died. Becker concludes that adolescents are unable to comply with the rigorous demands necessary to maintain euglycaemia with CSII. Schiffrin suggests that for diabetic adolescents CSII is more effective and acceptable than intensified conventional treatment. Van Ballegooie has studied the use of CSII in pregnant women and concludes that most patients will continue with CSII after the birth of their child. Bougnères, studying CSII in youngsters, (age: 17-53 months) also describes a good acceptation of CSII.

One of the differences between these studies and ours is the moment at which CSII is started. The lack of a "diabetic" past (discussed further on in this chapter) may contribute to the good acceptation of CSII. Further, a very trivial factor may contribute to the acceptation of CSII in Holland: its rather cool climate! Most hesitations towards continuation of CSII have been expressed during the summer (especially during periods of hot weather). Visibility and increased activities such as swimming, beach visits etc. may be involved.

Only once a serious practical problem has occurred with CSII:

the detachment of the needle from the catheter, necessitating surgical removal of the needle. This did not result in metabolic disregulation. Considering the problems and risks described by other authors, the incidence of problems in our CSII group is low (Anonymous 1985, Fishman 1981, Teutsch 1984). No differences are found between the CT and CSII group regarding the metabolic disregulations, including severe hypoglycaemia (once in both groups) and ketoacidosis requiring hospitalization (none in both groups).

Data on the risks of metabolic disregulations associated with CSII treatment are conflicting (KROC Collaborative Study Group 1985, Mecklenburg 1982, Mühlhauser 1985, White 1983). Mecklenburg and Mühlhauser find a relatively low incidence of severe hypoglycaemia in CSII patients (respectively 3 times in 100 patients during 500 patient-months and 12 times in 8 of 50 CSII patients during 1093 patient-months), which is more or less consistent with our results (1 time in more than 360 patient-months). Mühlhauser mentions the mismanagement of insulin therapy as main reason for the occurrence of the hypoglycaemic episodes. In our study this has also been the cause (too early administration of the insulin bolus). It stresses the importance of intensive patient (and parent) education. In CT patients the frequency of hypoglycaemic periods also seems to decrease with increased patient education (Casparie 1985). This suggests that the intensive patient education (by the nurse practitioner) and care may play an important role in the relatively low incidence of problems with CSII therapy and metabolic disregulations.

White describes 48 occasions of severe hypoglycaemia in 8 of 22 CSII patients during 467 patient-months, mostly between 01.00 and 05.00 hours and seemingly unrelated to patient error or pump malfunction. These hypoglycaemic episodes may be due to an insufficient glucose counterregulation (Cryer 1983, Madsbad 1982a). Madsbad describes an impaired reaction to glucagon in diabetic patients (adults) without residual insulin production. Although only the combination of an impaired reaction to glucagon and an insufficient production or effect of epinephrine will provoke an impaired counterregulation, the influence of the duration of IDDM can not be excluded (Madsbad 1983).

Contrary to other studies, the pump children in our study are studied during the first 2 years of IDDM. CSII has never before been started in unselected newly diagnosed diabetic children. The difference in duration of IDDM may explain the difference between the incidence of hypoglycaemia in the study of White and our study.

The KROC Collaborative Study Group finds an increased incidence of ketoacidosis in CSII patients. Since only regular insulins are used in CSII this may possibly be due to a lack of insulin depot. Pump failure, for example, (or patients' mismanagement) may thus provoke a ketoacidosis in a relatively short period of time. The difference between the KROC study and our study may be explained by the difference between the duration of IDDM among the participating patients. Madsbad has demonstrated, that the presence of an endogenous insulin production is associated with a later appearance of ketonbodies in insulin withdrawal

studies, thus delaying the development of a ketoacidosis and providing time for intervention (Madsbad 1979, Madsbad 1982b). Most of the children, participating in this study will have some C-peptide production left, since they only have been diabetics for a short period of time.

It can not be excluded that the age of the patients plays a role in the relatively low incidence of problems and metabolic disregulations. Children are more closely watched by parents and their family. This may result in earlier intervention in case of imminent ketoacidosis.

The time cost or required attention, assessed by the frequency of phone calls and home visits made by the nurse practitioner, does not differ between the 2 groups. During intercurrent infections CSII patients (or parents) request slightly less attention (compared with the CT children). This suggests that CSII indeed facilitates adjustments. Our observation is contrary to other studies, which emphasize the extra time-consuming aspect of CSII in children (Becker 1984, Bougnères 1984). Both studies describe CSII use in selected patients (adolescents and youngsters respectively) with a longer duration of IDDM (3.75 - 14.5 years and 5 - 27 months). The participants of our study are unselected, of all ages (1 - 16 years) and treated from diagnosis onwards with CSII. Absence of selection may be accompanied by a lack of motivation and motivation has been mentioned as an essential factor to successful CSII therapy (Raskin 1982, Stein 1982). One has to realize that the selection of patients is often based on poor metabolic control, brittleness and threat of complications. Such criteria indicate that the patients have already been through a considerable number of problems. Sometimes lack of alternatives, insufficient amelioration by intensified injection therapy, leads to the start of CSII. CSII may even be mentioned as "the last possibility". It is evident that despair and high-pitched expectation can influence the outcome of the therapy, the acceptation and the time cost. Our patients start with CSII at onset. During the first weeks, newly diagnosed patients, whether treated conventionally or by pumps, require an intensive training program. The acquisition of the technical aspects, activities and adjustments surrounding CSII therapy, may proceed more easily at this point of time. Getting used to things when one is young makes it easier when one gets older. Thus, starting at onset of IDDM with CSII is probably contributing to the low incidence of problems, disregulations, the good acceptation and the absence of an increased time cost.

In summary, CSII therapy is feasible in unselected newly diagnosed diabetic children. Three important factors, which probably contribute to this, are intensive patient education, the moment at which therapy is started (presence of endogenous insulin production and the absence of a burdened past) and the age of the patients. To what extent the presence of an endogenous insulin reserve or the lack of a "diabetic past" contribute remains to be elucidated. A careful follow-up of the participating children regarding these 3 aspects may give in time a further clari-

fication.

Psychological impact

The results of the psychological tests give no reason for not continuing CSII in unselected newly diagnosed diabetic children.

Since these tests have been taken by only 15 children (having completed the 2 years of follow-up), the results are preliminary and have to be evaluated with caution.

A significant difference in age is found between the tested children of the 2 groups (CT group: 14.9 ± 1.0 years; CSII group: 9.3 ± 1.2 years). A possible explanation for the increased difference is that only the first part of the children has been tested. At that time, 2 youngsters (2 and 5 years of age) dropped out because of the size of the available pump (Autosyringe AS6C). This difference in age implies a discrepancy between the level of psychological development and maturation and varying age-related problems.

Although the difference in age is considerable and possibly influenced by the 2 drop outs, the intelligence of the 2 groups of children is not different.

The Junior-Dutch Personality Test reveals no differences between the 2 groups regarding its 5 items: inadequacy, recalcitrance, dominance, perseverance, social inadequacy. The normal scores of both groups for social inadequacy suggest that neither of the treatments has formed an impediment for the social contacts and activities of the children. Compared with normal children the CSII group scores high for recalcitrance and dominance. Recalcitrance (related to negative feelings and distrust towards others) may form part of the (normal) coping response and acceptation process (Van den Burg 1985). Kovacs concludes in her recent publication that the acceptation process of IDDM in children lasts about 9 months (Kovacs 1985). Her results suggest that this acceptation process may be prolonged by CSII therapy. One can not omit however that a high score for recalcitrance points towards an increased feeling of inferiority. Considering the concern of healthy adolescents for their body and self-image, it may not be surprising that the onset of IDDM and a constant confrontation with the disease through the (visible) pump interferes with this process in a negative manner (Sullivan 1978). However, because of its easy adjustments, CSII therapy permits participation in most activities of the peer group and imposes less strict rules for day-to-day life. Therefore this may lead to a more complete self-image (Seigler 1982, Stein 1982). The high scores of the CSII group, when compared with reference values, for dominance (suggesting self-confidence and a tendency to bossiness) may support this point of view.

The use of CSII has no negative influence on the family or its functioning, as is assessed by the Family Relation Test (FRT), (looking through the eyes of the child) and the Family Environmental Scale (giving the parents' opinion (FES)). The CSII children express more negative feelings towards their mothers. Although the parents score in the normal range for the FES, they

do differ with respect to each other on two items. The mothers of the CSII group have the impression that they exert less control on the family, whereas the fathers of the CSII group experience more structure and organization in their family. These results may induce the speculation that age plays an important role. For the CSII children the beginning of the stormy period of adolescence, the striving for independence and liberation from emotional childhood is complicated by the onset of a chronic disease. Normal conflicts with the parents may be intensified because of the restrictions caused by IDDM. The more outspoken negative feelings of the CSII children towards their mothers as well as feeling of "lack of control" of the mothers may be provoked by the fact that mothers are more often involved in every day life including the diabetes regime.

The Diabetes Questionnaire, specifically designed for the 2 groups of diabetic children, reveals a significant difference regarding the incidence of physical complaints. The CSII group suffers less from physical complaints. This may stimulate their activities. The test confirms the lack of difference between the 2 groups with respect to their social activities and friends.

The Assessment of Acceptation Scale reveals a difference between the 2 groups concerning the physical health and metabolic control. The CSII group is considered to have a better metabolic control and a better physical health. The acceptation of the disease is considered similar by the parents. Compliance to advices of the diabetes team is only considered better in the CSII group by the fathers. Mothers and diabetes team members (2 of the 3) do not endorse this point of view and suggest that compliance does not differ. As for the psychical health of the children the observers present differing opinions.

It is evident that more data are necessary to evaluate the psychological impact of CSII. The data obtained thus far clearly indicate that CSII does not impede the children in their social activities and contacts. This is in accordance with the preliminary data on the psychological influence of pump therapy, described by Shapiro (Shapiro 1984). The physical well-being of the CSII group is significantly better. To what extent CSII contributes to psychological development remains to be elucidated in the following years.

Recommendations

First of all, the remaining children who have not completed the 2 years of the study, must be tested psychologically before more definite conclusions can be drawn.

In order to obtain information considering the long-term feasibility of CSII, a careful follow-up of the 30 children after the 2 years of the study is necessary. The psychological impact of long-term CSII therapy, started from diagnosis onwards, has to be evaluated by testing the children after 5 and 10 years.

METABOLIC CONTROL

The diabetic children, treated from diagnosis onwards with CSII, have a significantly better metabolic control when compared to the CT group with respect to sHbA1 values. The CSII group obtains sHbA1 levels in the near normal range. Intermediary metabolites, nor the other parameters for the metabolic control differ significantly. A possible explanation for this difference in sHbA1 is the more physiological way of administering insulin. The ease with which insulin administration can be adjusted with CSII may shorten hyperglycaemic periods and thus improve the control. Our finding is in accordance with the data of Madsbad, who studied the effect of CSII in newly diagnosed diabetic adults (Madsbad 1985). Whether this difference will persist in time remains to be studied. Mecklenburg states that the improvement of the metabolic control can be maintained in long-standing diabetics with long-term CSII therapy (Mecklenburg 1985). However, data concerning long(er)-term efficiency of CSII therapy in long-standing diabetics are conflicting (Becker 1984). Contrary to Mecklenburg, Becker demonstrates only a temporary improvement of metabolic control in long-standing diabetic adolescents. Although the data we have accumulated so far suggest a continuation of the better metabolic control (with respect to sHbA1), long-term efficacy of CSII remains to be proven. The importance of poor metabolic control with respect to the development of major diabetic complications remains uncertain. It has been demonstrated in an animal model that intensified insulin therapy reduces the development of retinopathy (Deneault 1980). The use of CSII therapy, from diagnosis onwards, may offer the opportunity to evaluate the influence of near normoglycaemia on the development of complications in human subjects.

Especially with respect to major complications and the possible beneficial effect of near normoglycaemia, it is important to focus on a special category of children: the very young diabetic children (5 years of age and younger). In these children major complications are likely to become manifest before the age of 40. It is very difficult to obtain even an acceptable metabolic control in these children. An explanation for this may be found in the age-related problems:

- long overnight pauses (19.00 - 07.00) without food intake
- a relatively high insulin sensitivity (Rosenbloom 1975)
- lipodystrophic injection sites
- frequent intercurrent diseases
- unpredictability of their activities.

Overnight metabolic profiles of these children add, as an extra problem, an even more outspoken early morning rise of blood glucose levels, or the so-called dawn phenomenon, when compared to diabetic adults (De Beaufort 1985). Regardless of its cause, it certainly contributes to the poor metabolic regulation of these children. Considering the age-associated problems and the night-profiles (referred to above) it may be possible to obtain an im-

provement in their metabolic control by using CSII therapy. The recent publication of Bougnères, studying CSII therapy in youngsters, demonstrates an improvement of their metabolic control (Bougnères 1984). An evaluation of the metabolic control in the 4 youngsters of our study (two of 1 year of age and two of 3 years of age: one of each in both groups) reveals a clear difference between the mean sHbA1 values of these children during the first year (excluding the first 2 months (CSII group: 9.3 and 9.4%; CT group: 11.5 and 12.3%)). This together with the results of Bougnères suggests that near normoglycaemia may be obtained in very young diabetic children by the use of CSII. Although a careful follow-up of these children is necessary to obtain information on the long-term effects of CSII on metabolic control and to evaluate its psychological impact, CSII therapy can be recommended for toddlers in order to obtain good metabolic control.

Improved metabolic control is not associated with an increased frequency of home blood glucose measurements. Regarding the quantity of test strips declared to the insurance companies, the suggestion is raised that the CSII group performs slightly less blood glucose measurements at home. Although the course of the sHbA1 does not show a significant difference between the 2 groups with respect to the variations in these sHbA1 percentages, the tendency towards less measurements may point to a more stable control. Since the data are incomplete, no definite conclusions can be drawn.

The intermediary metabolites are slightly increased in both groups when compared to healthy subjects. The 2 groups do not differ with respect to each other. Tamborlane describes a total normalization of the intermediary metabolites in children during the use of CSII (Tamborlane 1979). The difference may be explained by the fact that his study was performed in the hospital and lasted only 2 weeks.

The insulin doses do not differ between the 2 groups. This suggests that the same doses, administered in different ways, exert a distinct influence on the metabolic control. One must realize, however, that insulin dosage is not necessarily the same as insulin requirement. With the conventional therapy one is limited to increasing the insulin dose. It may reduce the hypoinsulinaemic periods but at the cost of an increased frequency of hyperinsulinaemia and hypoglycaemic periods.

The difference between the CT and CSII group regarding the relationship between insulin dose and insulin effect is also suggested by the difference in relationship between the insulin dose and the endogenous insulin reserve. It is uncertain which factors are involved in this relationship. Although the difference is not significant it suggests a better association in the CSII group between the endogenous production and the exogenous administration of insulin. In other words, they may be better attuned to each other. Insulin resistance may contribute to the difference between the two groups.

The importance of insulin resistance in IDDM has been stressed by DeFronzo (DeFronzo 1982). By employing the insulin clamp

technique he demonstrates a diminished insulin-mediated glucose metabolism in 19 insulin requiring diabetics compared with age and weight matched controls. Rizza and co-workers demonstrate (using the euglycaemic clamp technique) that hyperinsulinaemia, produced by the infusion of insulin, can create insulin resistance in man. He suggests that the decrease in insulin action probably occurs at a post receptor site (Rizza 1985). Although this study has been performed with healthy subjects, a possible implication is that hyperinsulinaemia, induced more outspokenly by conventional injection therapy, may impair insulin action, thus contributing to the difference in relationship between insulin dose and insulin effect. Conflicting with this is the study of Pernet, comparing insulin resistance in insulin requiring subjects and healthy controls. He suggests that impaired insulin sensitivity in IDDM is dependent on the insulin concentration. Using the euglycaemic clamp technique he demonstrates that at physiological insulin concentrations insulin requiring diabetic patients are resistant to insulin when compared with non-diabetic subjects. Supraphysiological levels of insulin, however, result in a disappearance of the difference between the diabetic and the healthy subjects (Pernet 1984). This suggests that hyperinsulinaemia may reduce insulin resistance. The conflicting data regarding insulin resistance emphasize the importance of further investigation.

Other studies suggest that not only hyperinsulinaemia but also hyperglycaemia may be involved in insulin resistance. Unger postulates that hyperglycaemia can impair peripheral insulin-mediated glucose transport (Unger 1985). This may also play a role in our study, since the CT patients have higher sHbA1 values and thus can be expected to have higher blood glucose values. Two studies describe an increased insulin sensitivity (using the clamp technique) after the start of CSII therapy and the achievement of an improvement in metabolic control (Beck-Nielsen 1984, Lager 1983). To what extent these factors (hyperinsulinaemia and hyperglycaemia) interrelate in insulin resistance in insulin requiring diabetic children remains to be elucidated.

It can be argued that part of the insulin resistance is due to circulating antibodies against insulin. DeFronzo finds no relationship between the presence of antibodies and insulin resistance (DeFronzo 1982). In our patients no relationship has been found between the presence of antibodies and metabolic control or the insulin dose. The presence of antibodies which interfere with the insulin receptor has not been studied (Maron 1983). Maron describes the presence of IgM antibodies at onset of IDDM in childhood, which exert an insulin blocking or an insulin-like effect on fat cells. These antibodies may alter the effect of a certain insulin dose.

Taken together, CSII therapy in newly diagnosed diabetic children results in a better metabolic control with respect to sHbA1. A more physiological administration of insulin and faster adjustments of hyperglycaemia may contribute to this difference. Since in small children (age: 5 years or younger) specific problems are present, which complicate the achievement of a good

metabolic control, CSII therapy is recommended for this group of children. The lack of difference in insulin doses used by the 2 groups may be explained by the fact that insulin dose is not the same as insulin requirement. This finding, in combination with the not significant, but suggestive difference between the 2 groups in relationship between insulin dose and endogenous insulin production, may point towards an increased insulin resistance in the CT group. To what extent hyperinsulinaemia, hyperglycaemia, immunological factors or yet unknown factors contribute to the occurrence of insulin resistance must still be found out.

Recommendations

Prevention of the late complications of diabetes in man by the near normalization of blood glucose concentrations has not yet been demonstrated since until recently, normoglycaemia could not be sustained from onset of IDDM onwards with the available methods of treatment (Tchobroutsky 1978). It has been shown that progression of present retinal abnormalities can not be prevented nor delayed by near normoglycaemia (Van Ballegooie 1984, KROC Study Group 1984, Lauritzen 1983, Tamborlane 1982). With these studies however, a point of no return was possibly passed already. Elevated albumin excretion has declined during CSII treatment toward the normal range, suggesting that an intensified treatment may retard progression of clinical nephropathy (KROC Collaborative Study Group 1984, Viberti 1979).

A careful long-term follow-up of the participants of the pump study may provide information on the effect of CSII on these complications. To obtain significant differences between the two groups in such a long-term study is probably not possible considering the small number of participants.

Parameters for metabolic control and endogenous insulin production as well as early detection methods for the onset of chronic complications have to be determined at regular intervals. Since the children will leave the Diabetes Clinic at about 18 years of age this interval can not be too small.

It seems feasible to obtain annually 24 hours urine for the determination of UCP and blood for the measurement of sHbA1 and lipid metabolites (HDL cholesterol and cholesterol as possible parameters for macroangiopathy).

For an early detection of retinopathy several techniques can be applied by the ophtalmologist. Fundus photos and fluorescein angiography may provide useful information on the development of early retinal abnormalities. Since the first signs of retinopathy are usually not seen until after 10 years of diabetes an ophtalmological test after 5 years of IDDM seems justified.

It is evident that the development of any reliable tool for early (or earlier) detection of complications has to be evaluated and, if possible and useful, applied.

The development of nephropathy can be studied by the measurement of micro-albuminuria and bloodpressure (Mogensen 1984). These parameters in combination with plasma creatinin and ureum concentrations will give further information on the development

of possible complications.

Neuropathy may occur at different periods of time after clinical onset. In adults it may even be the first symptom of IDDM. A relationship between neuropathy and the metabolic control has been suggested in several studies (Greene 1985, Young 1983). This is confirmed by others who show a reduction of the neuropathic symptoms after an important improvement in metabolic control (Van Ballegooie 1984, Spijker 1984). Tendon reflexes, position sense (position of the big toe) and vibrations sense can easily be tested during a visit to the Diabetes Clinic. Polyneuropathy, especially of the long sensible nerves of the legs, is often one of the first symptoms of neuropathy. The measuring of nerve conduction velocity is an established method to evaluate the neuropathy, an unpleasant one however, especially for children. Recently a new method has been developed by the neurologists of the Free University of Amsterdam. With their method the temperature sense is tested in a very sophisticated way (Bertelsmann 1985). It provides information on the functioning of the long thin sensible nerve fibers. Since this test is not painful and requires no extra injections etc. it is included in the parameters for the evaluation of neuropathy, together with the tendon reflexes, position sense and vibration sense. These parameters also ought to be determined once a year.

Thus for the follow-up of the participants of the pump study - in order to obtain information on the influence of CSII on the chronic complications - the following is suggested:

the determination, at least once a year, of:

- sHbA1, plasma HDL cholesterol, plasma cholesterol levels
- UCP (until no UCP is detected anymore, then the measurement can be stopped)
- Fundus photos
  Fluorescein angiography of the retina
- Blood pressure
  Plasma ureum levels
  Plasma creatinin levels
  Micro-albuminuria
- Tendon reflexes
  Position sense
  Vibration sense
  Temperature sense

The non-significant, but suggestive difference between the CSII and CT group with respect to the relationship between exogenous insulin administration and endogenous insulin production may raise the question to what extent this difference is caused by insulin resistance. In children its relevance has not been studied since the accepted method to study insulin resistance in vivo is the clamping technique. This can not be done with children (one has to lay calmly on a bed for at least 4 - 8 hours!). Although not providing the same quality of information the i.v. glucose tolerance test may be useful. The evaluation of the data obtained through this test, will provide information on the ef-

fect of a glucose load on the plasma glucose levels in the presence of a certain insulin concentration (Srikanta 1983). C-peptide levels provide information on the residual beta cell activity.

To evaluate the influence of immunological factors on the relationship insulin dose versus effect, antibodies, interfering with the effect of insulin on the fat cell, can be studied. Now the insulin receptor has been synthesized, the presence of these antibodies can be demonstrated by an insulin receptor assay or by bioactivity in the fat cell (Maron 1983). Separation and purification of the relevant IgM and IgG fractions may lead to the identification of these antibodies and elucidate their contribution to insulin resistance or even their possible involvement in the remission period.

REMISSION PERIOD AND ITS INDIVIDUAL PARAMETERS

The individual parameters of the remission period

An analysis of the individual parameters which characterize the remission period, reveals that only sHbA1 and the moment at which it deteriorates differ significantly between the 2 groups. The decrease in UCP and the increase in insulin dose past their critical values do not occur at significantly differing points of time. This confirms the preliminary data of a randomized trial with CSII in adults, recently presented by Madsbad (Madsbad 1985). The differences between our data and those of Mirouze may, next to the difference in age, be based on the randomization (Mirouze 1978). Mirouze studied a non-randomized group of adults.

The variability in UCP does not differ significantly between the 2 groups. UCP in time does not differ significantly between the 2 groups. One may speculate that the better glycaemic control in the CSII group causes suppression of the endogenous insulin production. Although this can not be excluded, the relationship between stimulated plasma C-peptide values and the urinary C-peptide excretion suggests a maximal functioning of the residual beta cells. The association between exogenously administered insulin and endogenous insulin production (on the Mood line) does not suggest a suppression either. CSII therapy results in a significantly less steep decline of UCP estimated through the slope. It is associated significantly more often with a peak (7 versus 3 times). The presence or absence of a peak in the initial course of IDDM does not show any relationship to the remission period. It is questionable whether this phenomenon has any importance at all, since no relationship with any of the other parameters for UCP has been detected. Peaks do not indicate a better residual beta function since the maximal UCP does not differ between children with or without peaks. A peak signifies that the course of UCP during the first year can not be characterized by simply drawing the Mood line. The presence of such a peak may contribute to the difference in the slope of the lines since - in the presence of a peak - the Mood line will be drawn from the end of the peak onwards.

A significant relationship is found between UCP at onset and after 1 year. This confirms the data of Koivisto, suggesting that the moment at which IDDM is diagnosed is vital for the course of the disease (Koivisto 1984). Although the coefficients of correlation of the 2 groups are not significantly different, the better correlation in the CSII group may suggest less interference by other factors (therapy related?). The presence of this relationship stresses the importance of an early diagnosis in order to start with as much endogenous insulin as possible.

Distinct to several other studies we could not identify a fixed relationship between the endogenous insulin production and the metabolic control (sought by the Pearson Contingency coefficient) (Ludvigsson 1977, Madsbad 1980, Schober 1980). It is interesting however, that only in one child sHbA1 within the normal range is not combined with UCP above 30%. In all other children an increase in sHbA1 (during a longer or shorter timespan) went with a decrease in UCP. Thus, the influence of (near) normoglycaemia on the preservation of the beta cell function can not be excluded.

The significant negative correlation between UCP (on the line) after 6 and 12 months and the insulin dose at these points of time has been discussed in the previous paragraph.

The remission period in IDDM has been defined in this study as a period, occurring after the onset of IDDM, with a near normal glycaemic control (sHbA1 $\leq$9.0%), an insulin dose below 0.5 U/kg bodyweight/24h and an endogenous insulin production resulting in a UCP above 30%. Pump therapy results in a significant prolongation of the remission period when compared to CT.

This effect is temporary however, and seems only to be "putting off the evil moment" for a short while (4 months). Evidently CSII therapy in children does not check the process causing IDDM. It may only create a little more time between the overt onset of the disease and the moment at which the child is totally dependent on exogenously administered insulin.

What causes this delay and can we identify any factors relevant for the continuation of the ongoing process?

The characteristics of the two groups of children differ only with respect to the age at onset. The children in the CSII group are significantly older (9.5 $\pm$ 1.1 years in the CSII group vs 7.0 $\pm$ 0.9 years of age in the CT group). As mentioned previously this may be provoked by the 2 drop outs in the beginning of the study. Two young children (2 and 3 years of age) have not started with CSII because the pumps available at that point of time were too large for them.

The evaluation of the relationship between age at onset and the remission period and its individual parameters does not reveal an association, distinct to other studies (Eff 1978, Knip 1982, Ludvigsson 1977).

One has to realize that criteria for remission differ considerably between different studies. Knip and Ludvigsson have, for example, not included a parameter for endogenous insulin production. Metabolic control is assessed by the presence or absence of glucosuria. Next to the different criteria the difference may be

explained by the relative young age of our participants. The course of IDDM may be less directly related to the age at onset if the disease starts before a certain - critical - age (Deckert 1978).

Contrary to other studies, we could not demonstrate any relationship between the characteristics of the participating children (age, sex, HLA-Dr types) and the remission period or its individual parameters (Eff 1978, Knip 1982, Ludvigsson 1984, Ludvigsson 1985, Madsbad 1983). The combination of age and HLA-Dr types or sex and HLA Dr-types does not show a significant association either. It is possible that the number of children studied is too small to demonstrate these associations. Ludvigsson shows a relationship between a slower course of IDDM and HLA-Dr3 in a multicentre trial with over 700 patients. It is not surprising that this is not observed in our small group of patients.

Symptoms at onset, not differing between the 2 groups, show no association with the remission period or its individual parameters. This dissents from the retrospective studies of Ludvigsson and Knip who demonstrate a negative relation between the severity of the symptoms at onset and the remission period (Knip 1982, Ludvigsson 1977). Once again, the differences in definition may be involved. The explanation may also be sought in the relative mild symptomatology at onset in the present survey. Only one child had a serious ketoacidosis (pH < 7.2) at onset and two (other) children came to the hospital with a dehydration, requiring the infusion of fluids and electrocytes (however without a serious ketoacidosis). These three children have had no remission period.

Regarding immunological parameters, the 2 groups differ neither at onset, nor during the first year. The presence of ICCA, ICCA-CF and ICSA at onset, nor their course during the first year reveals any relationship with the remission period or its individual parameters, distinct to other studies (Mustonen 1984). Our data do not provide any further information on the possible role these antibodies play in the pathogenesis or course of IDDM.

The levels of insulin antibodies (IgGIa) determined with the method of Christiansen do not differ after 1 year of therapy. The human semisynthetic insulins clearly induce an antibody production. No difference can be found between the two treatments or between the use of only soluble insulin vs combinations of soluble with zinc or isophane insulins. Neither could an association be demonstrated with the HLA-Dr types and the antibody production (Reeves 1984). An interesting fact however is that the only child without HLA-Dr 3 and/or Dr-4 has an extraordinary high antibody titer. It is evident that more factors than insulin purity alone are involved in the development of insulin antibodies. The presence of insulin antibodies shows no relation to the metabolic control. This is in keeping with other studies (Asplin 1981, Peacock 1983).

Discriminating, however, is the presence of insulin antibodies (IgGIb, measured by the more sensitive method) in 9 children of

the 28 tested previous to therapy with insulin. Although a role of these auto antibodies in the pathogenesis of IDDM is uncertain, they may be marker of autoimmune beta cell damage, detectable before the overt onset of the disease (Asplin 1983, Kaplan 1984, Palmer 1983). In keeping with this is our finding that the children with IgGIb at onset show a significantly faster decrease of the UCP and a significantly lower UCP 1 year after onset of IDDM. This association suggests that these antibodies may indeed be involved in or are a marker for the ongoing beta cell destruction. To evaluate whether these antibodies are involved in or are markers for autoimmune beta cell destruction further in vivo and in vitro studies are necessary.

Summarizing, although none of the parameters of the study can be directly related to the remission period, the presence of IgGIb at onset and the UCP level at onset show a significant correlation with the endogenous insulin reserve after 1 year. The influence of the glycaemic control on the endogenous insulin reserve remains to be clarified.

Recommendations

The follow-up of the studied children during the second year and after the end of the study, as described in the previous paragraph, may reveal further information on the course of IDDM and the importance of near normoglycaemia regarding the preservation of beta cell function.

In the long-term more information may be obtained regarding the relationship between normoglycaemia and/or an endogenous insulin production and the development of major diabetic complications.

The significant relationship between the endogenous insulin production at onset and after 1 year stresses the importance of earlier detection of IDDM in order to start with a considerable endogenous insulin reserve.

The role of IgGIb in IDDM must be studied in in vivo as well as in in vitro studies. Our demonstration of a negative relationship between IgGIb at onset and UCP after 1 year has to be confirmed by other studies (with larger samples). Further it would be very interesting to test the effect of positive serum samples on perifused islets of Langerhans in the absence and presence of complement to evaluate if the function of the beta cells is altered by these antibodies (Kanatsana 1981, Ziegler 1972). A purification of the serum fraction with IgGIb may allow a further characterization of these auto antibodies and their role in the pathogenesis of IDDM.

GENERAL DISCUSSION

Feasibility aspects and psychological impact of CSII in randomized newly diagnosed diabetic children do not form an impediment for the continuation of this method of insulin administration, but rather the contrary. Metabolic control is impro-

ved with respect to sHbA1. The remission period lasts about 4 months longer. Prolongation of the remission period is only temporary. The initial endogenous insulin reserve shows a significant correlation with the production after 1 year, suggesting no direct benefit of CSII therapy. Although the time costs of CSII are relatively low, the financial costs are considerable.

These results of the pump study evoke the question whether it is worthwhile to start with CSII in all newly diagnosed diabetic children, provided that the setting fulfills certain requirements (24 hours telephone service, education program, self-monitoring and a home visiting nurse practitioner).

Although it has not yet been proven that chronic complications can be prevented or delayed by good metabolic control (from onset onwards), CSII may contribute to a reduction of some chronic complications. No results from studies are available evaluating the effect of good metabolic control from diagnosis onwards. Most studies investigating the relationship between chronic complications and CSII are performed only after the first signs of complications have become manifest. One may think: too late already. In time our pump study may answer, or at least give an indication (because of the small number of participants) of the effect of CSII, started in an earlier phase, on the microvascular complications. A careful follow-up of the two groups regarding chronic complications is necessary and may provide relevant information concerning this.

At this point of time the results of the study do not justify the starting of CSII in all newly diagnosed diabetic children, however with 2 exceptions.

Firstly, 1 category of newly diagnosed diabetic patients ought to start with CSII, namely the youngsters with an age at onset of 5 years or younger. Their age-related problems contribute to the usually poor metabolic control. Considering the reduced life expectancy, the age at which the chronic complications may arise and taking account of the possible benefit of a good metabolic control, the use of CSII treatment as early as possible seems justified in this group of patients.

Secondly, if further development of the knowledge of the pathogenesis of IDDM results in the production of an adequate intervention therapy, CSII may be useful as interim therapy to obtain good metabolic control and to prolong the remission period temporarily.

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APPENDIX I

Request for confirmation of the parents' oral consent for participation of their child in the pump study

Dear Parents,

We would hereby like to thank you for your willingness to participate in the diabetes study.

For the sake of clarity and perhaps superfluously, we would like to briefly inform you of what it is about.

Every diabetes patient must have insulin administered his entire life. Until now the insulin used has been prepared from porcine or bovine. In the past few years, semi-synthetic human insulin has been produced abroad. Although this has been used, amongst others in the U.S. and Denmark, it is not yet available in the Dutch pharmacies.

We think that this insulin might be superior. In order to confirm this, research is necessary. All children participating in this research project will be treated with human insulin.

Another part of this research project involves the method of administering the insulin. In order to imitate the normal situation as much as possible, there are currently pumping devices which provide a constant release of insulin into the body over a period of 24 hours. This method would provide a close imitation of a normal condition. However, research regarding this is necessary first. At random is determined which patient (in the event permission is granted for participation in the project) receives the conventional treatment (1 x or 2 x an insulin injection daily) and which patient receives the pump treatment. Small children may not be considered for the pump treatment.

Participation in this project means that blood sampling will take place more frequently, to wit:

1st month : 1 x per week
2nd month : 2 x per month
3rd month - 2 years: 1 x per month.

Once every month 24 hours urine has to be collected on ice.

At any time you can approach us with further questions (phone number: 010 - 656566, ext. 1110).

We would kindly request you to notify your approval of the project and the participation of your child in this project by signing the enclosed paper.

It is emphasized once again, that you have the right to stop this participation at any time during the study, with no explanation required.

Hoping to have informed you sufficiently and thanking you again, we remain,
yours sincerely

C.E. de Beaufort

G.J. Bruining (pediatrician/endocrinologist)

APPENDIX I (continued)

Undersigned: Born:

Parent(guardian) of: Born:

declares to have taken note of the participation of

in a study in which human insulin and/or insulin pumps are studied.
Undersigned has been notified of the fact, that all patients will use human insulin, but that at random is determined which child starts with the pump and which with the conventional injection therapy.
Small children may not be considered for the pump treatment.
Children and/or parents (guardian) have the right to stop the participation at any time during the study, with no explanation required.
The duration of the study and the possible risks and disadvantages of the study have been clearly explained before the start of the study.

C.E. de Beaufort child (>12 years)

G.J. Bruining (pediatrician/ endocrinologist) parent/guardian

APPENDIX II

Costs of the requisites for pump treatment (1a and 1b) and conventional treatment (2)

Requisites (per month = 30 days)			Costs as calculated by the purchase department of the SKZ	
1a Pump therapy			CPI Betatron 9204	
1 1/2 ml syringe+ needle			Hfl	90.44
Opsite (Hfl 8.10 - Hfl. 18.89) *			Hfl	18.89
Infusion set (Hfl 58.60 - Hfl 117.20) *			Hfl	117.20
Stopcaps (30 à 50)			Hfl	23.20
Insulin (actrapid) (Hfl 19.60 - Hfl 78.42)			Hfl	78.42
Medium (diluting solution)				-
Diaburstrips	o	(50)	Hfl	9.67
Keturstrips	o	(50)	Hfl	10.62
Hemoglucotest strips	o	(25)	Hfl	35.04
Monolets prickers	o	(25)	Hfl	15.82
Glucagon infusion set	o	(1)	Hfl	18.80
Range		Hfl 280.61 -	Hfl	418.10
Initial expense for the Pump + charger + batteries (3) (expected life span = 6 years)			Hfl	6.090.00

* Dependent on the frequency with which the infusion set is changed (5-7 days).

o Requisites for blood glucose monitoring at home, not paid by the project budget.

APPENDIX II (continued)

Requisites (per month = 30 days) for			Costs as calculated by the purchase department of the SKZ	
Ib Pump therapy			Autosyringe AS6C	
3 ml syringe (luer lock)			Hfl	12.32
2 ml syringe			Hfl	3.60
Needle			Hfl	6.68
Opsite (Hfl 8.10 - Hfl 18.89) *			Hfl	18.89
Infusion sets (Hfl 58.60 - Hfl 117.20) *			Hfl	117.20
Stop cap (30 à 50)			Hfl	23.20
Insulin (actrapid) (Hfl 19.60 - Hfl 78.42)			Hfl	78.42
Medium (diluting solution)				-
Diaburstrips	o	(50)	Hfl	9.67
Ketur strips	o	(50)	Hfl	10.62
Hemoglucotest strips	o	(25)	Hfl	35.04
Monolets prickers	o	(25)	Hfl	15.82
Glucagon infusion set	o	(1)	Hfl	18.80
Range:		Hfl 212.77 -	Hfl	350.26
Initial expense for the pump + Charger + 2 batteries (expected life span: 3 years)			Hfl	5.192.00

* Dependent on the frequency with which the infusion set is changed (3-7 days).

o Requisites for blood glucose monitoring at home, not paid by the project budget.

APPENDIX II (continued)

Requisites (per month = 30 days) for			Costs as calculated by the purchase department of the SKZ	
2. Conventional injection therapy				
2 ml syringe		(60)	Hfl	7.30
Needles		(60)	Hfl	3.60
Diabur teststrips	o	(50)	Hfl	9.67
Ketur teststrips	o	(50)	Hfl	10.62
20/800 hemoglucotest	o	(25)	Hfl	35.04
Monolets	o	(25)	Hfl	15.82
Glucagon infusion set		(1)	Hfl	18.80
Insulin (Monotard)		(Hfl 14.36 - Hfl 64.82)	Hfl	64.82
Actrapid		(Hfl 13.04 - Hfl 19.56)	Hfl	19.56
Range:		Hfl 128.25 -	Hfl	185.23

o Requisites for blood glucose monitoring at home, not paid by the project budget.

APPENDIX III

Items of the Dutch Personality Test for Juniors

Item		Interpretation
1. Inadequacy	- high score:	anxious, sense of inferiority, usually difficult in social contacts
2. Perseverance	- high score:	calm, conscientious child, positive attitude towards work and with perseverance
3. Social Inadequacy	- high score;	withdrawing from their peer group, inadequate in maintaining social contacts
4. Dominance	- high score:	self-confident (apparently sometimes dominating), not easily influenced by others
5. Recalcitrance	- high score:	negative and suspicious attitude towards others

APPENDIX IV

Items of the Family Environment Scale

Item	Interpretation
Cohesion	Concern of the family members for each other
Expression	Possibility to express feelings and opinions freely and directly
Norms and values	The attitude of the family members towards norms and values
Organization	The way in which rules, tasks or duties are handled within the family
Control	The control exerted by the family towards family members
Conflict	The expression of anger and aggression within the family
Social orientation	Concern of the family for the political and social sides of life
Recreation	Participation by family members in recreational activities indoors and outdoors
Ambition	The ambitions of family members

APPENDIX V

Items of the Diabetes Questionnaire

Items	Max. Score	Interpretation
Physical complaints	7	- poor metabolic control
Social contacts	7	- has poor social contacts
Injection fear	7	- is afraid of injecting itself
Socially restricted	9	- the diabetes impedes its activities and social contacts
Physically restricted	6	- the diabetes impedes physical activities, such as sports
Attitude outsiders	5	- outsiders are afraid of IDDM/injections, as observed by the child
Attitude parents	8	- parents are not overly concerned nor consider the child as pitiful
Dietary problems	5	- difficulties in accepting and complying to dietary rules
Wish to have children when grown up	2	- wish to have no children when grown up

APPENDIX VI

Diabetes Questionnaire

Name: Yes No

1. Sometimes I feel sick.
2. I often feel strange.
3. I often have a tummy ache.
4. I often wake up in the middle of the night.
5. Then I have to go to the bathroom.
6. I am then very very thirsty.
7. When I wake up in the morning I often have a headache.
8. I often have a runny bm (= bowel movement).
9. I have a lot of friends.
10. I often play with my friends.
11. Most of all I like to play by myself.
12. I often argue with my friends.
13. I like animals more than people.
14. Other children think I'm a nuisance.
15. I often dream about needles.
16. I think injections are terrible.
17. My father says, that I should be brave when I get an injection.
18. I think a prick in the finger is much worse than the injection.
19. My mother doesn't mind the injections.
20. My parents feel sorry for me because I have to have injections.
21. My friends don't mind the injections.
22. I never want anyone to see me getting an injection.
23. My friends always like to see me getting an injection.
24. I don't like to play at a friend's house if I still have to have an injection.
25. I can never play for very long at a friend's house, because of my injections.
26. My mother doesn't like my friends to see me getting my injection.
27. I am always hungry.
28. I like sweets and candy a lot.
29. My mother is a real good cook.
30. My mother feels sorry for me.
31. I get more presents because I have to have injections.
32. My mother gets mad at me, if I eat a piece of candy.
33. I'm never allowed to eat nice food.
34. My parents think it is pretty terrible because I can not eat just anything.
35. My father thinks that injections are just terrible.
36. My mother thinks that I am real brave.

APPENDIX VI (continued)

	Yes	No
37. Children, who have to have injections, should get a lot of presents.		
38. I want a lot of children when I grow up.		
39. I will never want children of my own.		
40. Injections are worse for children than for grown-ups.		
41. Grown-ups think injections are terrible too.		
42. My teacher thinks injections are real frightful.		
43. I don't like parties at all.		
44. I'm always invited to my friend's parties.		
45. I don't want to throw a party.		
46. I don't like to treat other children to sweets.		
47. When children are treated to sweets, I always get something else.		
48. I wish no one knew that I need injections.		
49. I am often afraid of getting an injection.		
50. My parents love me the most.		
51. I don't like to eat at my friend's house.		
52. I often tease other children.		
53. I like to swim a lot.		
54. I like PE (Physical Education).		
55. At home I like to wear my gym clothes.		
56. I don't like to swim.		
57. I don't like putting on my swimming suit at the swimming pool.		
58. I don't like getting dressed for PE at school.		

APPENDIX VII

Assessment of acceptation scale

Name of the critic: .....
Name of the child : .....

1. Indicate to what extent the child accepts its diabetes.

very good	-	good	-	moderate	-	bad	-	poor
1		2		3		4		5

2. Give your opinion on the metabolic control of the child.

very good	-	good	-	moderate	-	bad	-	poor
1		2		3		4		5

3. Give your opinion on the physical condition of the child.

very good	-	good	-	moderate	-	bad	-	poor
1		2		3		4		5

4. Give your opinion on the capacity of the parents to effectuate advices, given by the diabetes team. (This comprises as well the compliance of the parents as the influence of the parents on the child).

very good	-	good	-	moderate	-	bad	-	poor
1		2		3		4		5

5. Give your opinion on the psychological health of the child.

very good	-	good	-	moderate	-	bad	-	poor
1		2		3		4		5

APPENDIX VIII

Letter to the insurance companies, concerning the quantity of refunded blood test strip pots

Dear Colleague,

We kindly request your attention for the following.
In the past four years research has been conducted in the SKZ regarding the influence of CSII treatment on residual insulin production of insulin dependent diabetic children. For this purpose 30 newly diagnosed children have at random started with either CSII or conventional therapy. Besides the above mentioned we are particularly interested in the effect of CSII on metabolic control. Better metabolic control could lead to less frequent blood testing. In order to investigate the difference in use of blood sugar strips between the two groups, we kindly request your cooperation.
We would like to know if it is possible that you fill in the enclosed form as to how many pots of blood test strips have been declared by the patient (parents) during the relevant months.

Hoping that you can and will fulfill our request, and thanking you for your cooperation,
we remain
yours sincerely,

C.E. de Beaufort

G.J. Bruining (pediatrician)

NAME

Month	Blood strip pots	Month	Blood strip pots
1		1	
2		2	
3		3	
4		4	
5		5	
6		6	
7		7	
8		8	
9		9	
10		10	
11		11	
12		12	
Total			

SUMMARY

The influence of CSII on the remission period of newly diagnosed insulin dependent diabetic children is the central theme of this thesis. An answer is sought for following questions:

- Is CSII feasible in not selected newly diagnosed diabetic children? What is the psychological impact of the therapy?
- What is the influence of CSII on the metabolic control?
- Does CSII prolong the remission period of diabetic children? If so, which factors contribute to this?

In Chapter 1 motives and purposes of the study are briefly described. Progressive loss of insulin producing beta cells results in a metabolic disregulation. This leads to a lifelong dependency on insulin administration. Shortly after the start of insulin therapy a remission period may occur. The remission period is characterized by a good (near normal) metabolic control with a relatively low insulin dose. Some beta cells seem to recover temporarily. However, after several weeks or months insulin requirements increase once again. In insulin withdrawal studies the presence of a residual beta cell activity is associated with a later onset of metabolic disregulations. Chronic complications have often been suggested to occur less in patients with a residual beta cell activity. This has led to intensive research into possibilities to influence and/or prolong the remission period. Retrospective studies suggest a beneficial effect on this period of a rapid normalization of metabolism after the onset of IDDM. To obtain a good metabolic control in children often raises problems. In general, several injections per day (at least 2) are necessary, which is not always easy in children. The availability of CSII, however, offers new possibilities.

In order to evaluate the influence of CSII on the metabolic control and the remission period of newly diagnosed diabetic children, a prospective randomized study has been undertaken. Since CSII has never before been used in a group of not selected newly diagnosed diabetic children, the feasibility of this therapy has to be studied. The feasibility for the child, its parents and the medical staff are included.

In Chapter 2 IDDM, the pathogenesis and possible causes are discussed. Hereditary susceptibility, combined with a viral or environmental agent, may cause a disturbance of the immune system, possibly resulting in the autoimmune destruction of beta cells. For the patient it implies a lifelong dependency on insulin injections. Ten to 15 years after the onset of IDDM chronic complications may occur (nephropathy, retinopathy, neuropathy and cardiovascular abnormalities). It may not be surprising that this chronic disease exerts an influence on the psyche of the patients. Many factors - however - will be involved in the coping responses.

The remission period is discussed in more detail in the 2nd paragraph. During this period, occurring shortly after the start of insulin therapy, a good metabolic control is obtained with a relatively low insulin dose. In this thesis the remission period will be characterized by 3 parameters.

- a near normal metabolic regulation (sHbA, within the normal range)
- a near normal endogenous insulin production (urinary C-peptide excretion within the normal range)
- an insulin dose below 0,5 U/kg/24 hours

Morphological studies demonstrate beta cell hyperactivity and regeneration during the remission period. The metabolic disregulation, present at onset, is almost normalized. To maintain a good (near normal) metabolic control, a relatively low insulin dose is needed. This suggests either a recovery of insulin producing beta cells or an increased insulin sensitivity of the tissues. To what extent therapy contributes to the occurrence of the remission period remains to be clarified. The discovery of C-peptide (a peptide, which is secreted by the pancreas in equimolar quantities as insulin) and the development of an assay to measure it, offers the possibility to assess the endogenous insulin production. The relevance of an endogenous insulin production has been suggested by several studies. As mentioned before, a later onset of metabolic disregulation in insulin withdrawal studies as well as less chronic complications have been described in association with the presence of an endogenous insulin production. Rapid normalization of metabolism after the onset of IDDM is suggested to result in an increased occurrence and longer duration of the remission period. An association between age and seriousness of metabolic disregulation at onset and the occurrence of a remission period has also been described. To what extent other factors, such as immunological disturbances, are involved remains to be elucidated.

The aim of the pump study is to evaluate the influence of CSII on the metabolic control and on the remission period of diabetic children.

In Chapter 3 the aim of the treatment of IDDM children in the Sophia Childrens' Hospital (part of the University Hospital Rotterdam, Rotterdam) is described as well as the methods used to pursue this aim. In the Sophia Childrens' Hospital the diabetes team, consisting of a pediatric endocrinologist, a pediatrician, a nurse practitioner, a dietician and - during this study - a research fellow, takes care of about 150 diabetic children. The purpose of the treatment is achieving a good metabolic control, without hypo- or hyperglycaemic periods, and a normal development. Patient (and parent) education and self monitoring form the basis of the therapy. Hospitalization is reduced as much as possible. A 24 hours telephone service is imperative on offering children and parents the possibility to consult one of the

team members at any time. After the clinical onset of IDDM practical and theoretical instruction given by the nurse practitioner, if possible at home. This depends on the seriousness of metabolic disregulation, the social background (inter alia presence of a telephone) and the availability of the nurse practitioner. Later on home visits will be made for several purposes (a repetition of practical skills, instruction for holidays, pedagogical or psychological problems). Once a year parents of recently diagnosed children are invited to participate in a "refresher" course in the hospital (5 evenings).

At the start of this study only for 1 child a pump had been used. CSII is expected to imitate more or less the physiological insulin production (although insulin is still administered in the wrong place). Further experience with this therapy - however - is needed.

In Chapter 4 the design and protocol of the study are described in more detail. In a prospective randomized study 30 newly diagnosed diabetic children - consecutively referred to the Sophia Childrens' Hospital - are treated either with CSII or with CT. In both groups semisynthetic human insulin is used. Oral and written consent is obtained from parents (and children of 12 years of age or older). During 2 years the children visit the outpatient clinic monthly. The first 3 months these visits are more frequent. After 2 years of follow-up the children are tested psychologically. In this thesis the results after 1 year of follow-up are given. Since the psychological tests are only performed after 2 years of follow-up, these data are preliminary and incomplete.

At onset the seriousness of the metabolic disregulation is assessed by blood glucose levels, blood pH and ketonuria. HLA typing and virusserology have been performed to study their relationship with IDDM and its remission period. The feasibility of CSII in not selected diabetic children is assessed by 4 parameters:

- acceptation of the therapy by child (and parents)
- practical problems (and their possible consequences on the metabolic disregulation)
- frequency of telephone calls
- frequency of home visits by the nurse practitioner

Main parameter for the metabolic control is the monthly determined stable glycosylated hemoglobin (sHbA1). After 6 months and 1 year intermediary metabolites are measured. The frequency of blood glucose measurements at home and of hypoglycaemic periods are also included as parameters for the metabolic control, as well the insulin dose. Monthly determined 24 hours urinary C-peptide excretion is the main parameter for the endogenous insulin production. The glucagon stimulation test is performed once every half year to obtain information on the beta cell function after stimulation. The relationship between these 2 methods is discussed. A 95% reference interval for 24 hours uri-

nary C-peptide excretion has been calculated for healthy children of different ages. Islet cell cytoplasmic antibodies, complement or not complement binding, and islet cell surface antibodies have been determined at onset and after 6 and 12 months. Insulin antibodies have been measured by 2 methods at onset, Three, 6, 9 and 12 months after the onset they have been measured by 1 method (the slightly less sensitive "classical" one). Finally the statistical analysis is described.

In Chapter 5 the results of the study are given. Of the 34 consecutively referred children 4 dropped out. Two children were too small for the pumps available at that moment (the AS6C; the CPI betatron became available after about 1 year). One child got CSII instead of the planned CT, because of a positive family history. Finally one girl was treated conventionally instead of by CSII because of her social background. Age at onset differs significantly between the 2 groups. The children of the CSII group are older. The metabolic disregulation at onset does not differ significantly between the 2 groups. Pump therapy is well accepted. Only one girl has changed after 28 months from CSII to CT. Practical problems resulting in serious metabolic disregulations have not occurred. The CSII group has paid slightly less telephone calls. The frequency of home visits does not differ between the 2 groups. Only 15 children have been tested psychologically. With respect to physical complaints the 2 groups differ significantly. The CSII group expresses less physical complaints compared with the CT group. A significantly better metabolic control is found in the CSII group with respect to sHbA1. Intermediary metabolites do not differ. Blood glucose measurements are performed about as often in both groups. Hypoglycaemia is seen with equal frequency in both groups. Insulin doses do not differ either between the CSII and CT group. The urinary C-peptide excretion nor the stimulated plasma C-peptide values show a difference between the 2 groups. The C-peptide excretion at onset is significantly related with the C-peptide excretion after 1 year. The remission period lasts about 4 months longer in the CSII group. Age or degree of metabolic disregulation at onset, nor the presence of islet cell antibodies show an association with the occurrence of a remission period. A significant negative relationship is found between the presence of insulin antibodies (IgGb) before the start of therapy and the C-peptide excretion after 1 year. No fixed relationship has been found between sHbA1 and C-peptide excretion. Interesting is - however - that only once a decrease in C-peptide excretion is not preceded by an increase in sHbA1. Urinary C-peptide excretion and insulin dose show a significant correlation in both groups after 6 months and 1 year. The coefficients of correlation in the 2 groups show a suggestive, but not significant difference.

In Chapter 6 the results are discussed and compared with other studies. Recommendations for further research are given. Pump therapy has not before been used in not selected newly diag-

nosed diabetic children. Most studies describe the use of CSII in selected populations of diabetic patients with a longer duration of IDDM. Differences between the results, described in this thesis and the data of other studies are the time requirements (for the medical staff), the acceptation of the therapy and the occurrence of metabolic disregulations (hypo- and/or hyperglycaemia). Partly these differences can be ascribed to the moment at which therapy is started. The 30 participating children do not yet have a "diabetic" past. The presence of an endogenous insulin production may also play a role in the less frequent occurrence of metabolic disregulations. Further, the patients studied are children. Possibly the attention paid by the parents may contribute to an earlier intervention in imminent disregulation. The follow-up of the 30 children after the 2 years of the study may provide further information on these 3 factors and their individual importance.

Analysis of and discussion concerning the psychological tests are complicated, since the data are preliminary. CSII - however - does not seem to form an impediment for the children and their (social) activities. The role of an intensive education in the prevention of metabolic disregulations is widely accepted.

Regarding the metabolic control the CSII group shows a significantly lower sHbA1. In youngsters ($\leq$ 5 years) this improvement is considerable. Because of age dependent problems achievement of an acceptable control is very difficult in these children. CSII is of benefit for this group, since it offers the possibility to adjust more frequently and more adequately the insulin dose without increasing the injection frequency. The frequency of blood glucose measurements is significantly higher in most studies. The relatively low frequency of 5 measurements per week is not associated with an increase in metabolic disregulations. The moment at which the children are studied may also play a role in this difference.

Of interest are the same insulin doses of the 2 groups. One has to realize - however - that insulin dose and insulin requirements are not the same. Especially in the CT group the insulin dose can not always be augmented in order to reduce hyperglycaemia, for this may result in an increased occurrence of hypoglycaemic periods. To what extent a difference in insulin sensitivity is involved is unknown. Several studies suggest a better insulin sensitivity in CSII patients. Further (in vivo and in vitro) studies are needed to study this phenomenon in children. The follow-up of the children after the 2 years of the study may provide in due time information on the relationship between the occurrence of a remission period, the metabolic control and the onset of chronic complications. One must not forget - however - that only a small number of patients is studied.

No difference is found between the endogenous insulin production of the 2 groups. The significant relationship between the C-peptide excretion at onset and after 1 year has also been described by another study. It stresses the importance of an early diagnosis and start of therapy. The presence of insulin antibodies before the start of insulin therapy shows a negative

association with the C-peptide excretion after 1 year. Whether these antibodies are actively involved in the ongoing destruction of beta cell mass or are just "markers" for beta cell destruction is unknown.

The remission period lasts significantly longer (4 months) in the CSII group. Contrary to retrospective studies no association has been found between age and metabolic disregulation at onset and the occurrence of a remission period. This may be explained by the different definitions and criteria which are used. It can not be excluded that age only plays a role below or above a certain critical level. For the lack of association between the metabolic disregulation and the remission period the same explanation may be given, especially considering the fact that the 3 children, who needed intravenous administration of fluids and insulin have no remission period. None of the determined parameters shows a significant relationship with the remission period.

SHbA1 and C-peptide excretion show no fixed relationship. Still, only in 1 case a decrease of C-peptide excretion is not preceded by an increase in sHbA1. The relationship between insulin dose and endogenous insulin production differs slightly between the 2 groups. One could speculate that this difference suggests a different insulin sensitivity in the 2 groups. Insulin administered with CSII may be more effective (considering the lower sHbA1 percentages). Several other studies describe a higher insulin sensitivity in patients with CSII.

Finally, 2 indications for the use of CSII in newly diagnosed children are given. First of all, the youngsters (< 5 years) are considered as candidates for CSII therapy. Secondly, if methods are developed for intervention in the ongoing destruction of beta cells, CSII may be useful as interim therapy until intervention therapy is started.

Returning to the questions, mentioned at the beginning of the summary, following answers have been found:

- CSII is feasible in not selected newly diagnosed diabetic children. Thus far, preliminary results of the psychological tests do not show a negative influence of CSII on newly diagnosed diabetic children and their social activities
- with respect to sHbA1 the metabolic control in the CSII group is significantly better. The other parameters for the metabolic control including the insulin dose show no significant differences between the 2 groups
- the remission period lasts about 4 months longer in the CSII group.

No factors have been found, which show a significant relationship with the occurrence of the remission period. However, the C-peptide excretion at onset as well as the presence of insulin antibodies before therapy are significantly related to the endogenous insulin production (one of the individual parameters for the remission period) after 1 year.

SAMENVATTING

De invloed van continue subcutane insuline infusie (CSII) op de remissie periode van insuline afhankelijke diabetes mellitus (IDDM) op de kinderleeftijd staat centraal in dit proefschrift. Getracht wordt om de volgende vragen te beantwoorden:

- Is CSII toepasbaar bij nieuwe niet geselecteerde kinderen met IDDM? Wat is de psychologische invloed van deze behandeling?
- Resulteert CSII in een betere metabole regulatie van deze kinderen?
- Beïnvloedt CSII de remissie periode? Zo ja, welke factoren spelen daarbij mogelijk een rol?

In hoofdstuk 1 wordt weergegeven hoe en waarom dit onderzoek tot stand is gekomen.

Progressief verlies van insuline producerende beta cellen leidt door insuline deficiëntie tot uitgebreide stoornissen in onder andere glucose en vet metabolisme. Insuline injecties worden - levenslang - noodzakelijk. Snel na de start van deze therapie treedt in sommige gevallen een remissie periode op. Deze periode wordt gekarakteriseerd door een goede metabole instelling met een relatief geringe insuline dosis. De beta cellen lijken gedurende korte tijd ten dele te herstellen. Echter, na enige weken of maanden neemt de insuline behoefte (de hoeveelheid die nodig is om een zo normaal mogelijk metabolisme te handhaven) weer toe. Diverse studies suggereren dat de aanwezigheid van enige resterende beta cel activiteit geassocieerd is met een minder snel metabool ontregelen en mogelijk ook met minder chronische diabetes complicaties. Dit heeft geresulteerd in intensief onderzoek naar mogelijkheden om de remissie periode te beïnvloeden (en te verlengen). Retrospectief onderzoek geeft aanwijzingen voor een positieve invloed van een goede metabole regulatie, verkregen zo snel mogelijk na de start van de insuline therapie. Bij kinderen is het bereiken van een goede metabole regulatie een moeilijke opgave, mede door het feit dat vaak meerdere injecties (>2) per dag nodig zullen zijn. De komst van CSII opent echter nieuwe perspectieven.

Om na te gaan hoe CSII de metabole instelling en de remissie periode van nieuwe kinderen met IDDM beïnvloedt is gekozen voor een prospectief gerandomizeerd onderzoek (beschreven in dit proefschrift). Aangezien CSII nooit tevoren in een groep niet geselecteerde nieuwe patienten is gehanteerd, dient eveneens gekeken te worden naar de uitvoerbaarheid van deze therapie, in de eerste plaats voor het kind en zijn familie en in de tweede plaats voor het behandelend team.

In hoofdstuk 2 worden IDDM, de pathogenese en mogelijke oorzaken besproken. Erfelijke aanleg, gecombineerd met een viraal of ander agens, leidt waarschijnlijk tot een verstoring van het immuun apparaat. Deze resulteert in de auto immuun destructie van de beta cellen. Voor de patiënt betekent het een levenslange afhankelijkheid van insuline injecties. Tien tot 15 jaar na het begin van de ziekte treden in een aantal gevallen ernstige com-

plicaties op (nefropathie, retinopathie, neuropathie en cardiovasculaire afwijkingen). Dat deze chronische ziekte een invloed kan hebben op de psyche van de patient ligt voor de hand. Vele factoren kunnen hierin een rol spelen.

De remissie periode wordt in de 2e paragraaf uitvoeriger besproken. Met de remissie periode wordt een periode bedoeld, die vaak optreedt kort na de start met insuline therapie. Gedurende deze periode heeft de patiënt een goede metabole regulatie met een relatief geringe insuline dosis. In dit proefschrift wordt deze periode gekarakteriseerd door 3 parameters:

- de metabole regulatie (in de normale range)
- de endogene insuline productie (in de normale range)
- de insuline dosis (< 0.5 E/kg/24 uur)

Morfologische studies tonen in deze periode hyperactiviteit en regeneratie van de beta cellen. De metabole ontregeling aanwezig bij de ontdekking van IDDM is weer (bijna) genormaliseerd en voor handhaving van een goede metabole regulatie is slechts een geringe insuline dosis nodig. Dit lijkt te wijzen of op een herstel van beta cel activiteit of op een toegenomen gevoeligheid voor de toegediende insuline. Het is niet duidelijk in hoeverre deze periode door de therapie wordt beïnvloed. De ontdekking van het C-peptide (een eiwit, dat in even grote hoeveelheden als insuline wordt uitgescheiden door de pancreas) en de ontwikkeling van een bepalingsmethode hiervoor biedt de mogelijkheid om de endogene insuline productie te meten. Het belang van endogene insuline productie wordt gekenschetst door al eerder genoemde bevindingen. De aanwezigheid van enige endogene insuline productie lijkt geassocieerd te zijn met een minder snel metabool ontregelen. Eveneens zouden mogelijk minder frequent chronische complicaties optreden in aanwezigheid van een endogene insuline productie.

Retrospectief onderzoek wijst op een positieve associatie tussen snel normaliseren van het metabolisme na de ontdekking van IDDM en een vaker optredende en langer durende remissie. Eveneens wordt een associatie beschreven tussen de leeftijd en het voorkomen van een remissie periode (hoe jonger des te korter en minder frequent). In hoeverre andere factoren, zoals immunologische, een rol spelen in het voorkomen van de remissie periode is nog onbekend. Het doel van de in dit proefschrift beschreven studie is na te gaan wat de invloed van CSII is op de metabole regulatie en op de remissie periode van kinderen met IDDM.

In hoofdstuk 3 worden de doelstellingen van de therapie en de methode waarop deze nagestreefd worden in het Sophia Kinderziekenhuis, beschreven. In het Sophia Kinderziekenhuis (deel van het Academisch Ziekenhuis Rotterdam) draagt het diabetes team, bestaande uit 1 kinderarts-endocrinoloog, 1 kinderarts, 1 gespecialiseerde verpleegkundige, een diëtiste en - voor de duur van het onderzoek - een arts, zorg voor ongeveer 150 kinderen met IDDM. Het doel van de behandeling is om een goede metabole regulatie te krijgen, zonder hypo- of hyperglycaemie en met een normale ont-

wikkeling. Patiënt- en oudereducatie en zelfcontrole met behulp van bloedsuikerbepalingen vormen de grondslag voor een goede behandeling. Getracht wordt ziekenhuisopnames zoveel mogelijk te beperken. Een 24 uurs bereikbaarheidsdienst van een van de teamleden is hiervoor noodzakelijk, opdat ouders en/of patiënt bij onverwachte problemen contact op kunnen nemen voor overleg.
Na de ontdekking van IDDM wordt de eerste praktische en theoretische instructie zo mogelijk thuis gegeven door de gespecialiseerde verpleegkundige. Dit is ondermeer afhankelijk van de mate van ontregeling van de patiënt, de thuissituatie (aanwezigheid van telefoon) en de beschikbaarheid van de gespecialiseerde verpleegkundige. In de loop der tijd worden onder meer voor herhaling van praktische technieken, vakantie instructie en pedagogische en/of psychologische problemen huisbezoeken gebracht. Ongeveer een half tot 1 jaar na de ontdekking van IDDM worden de ouders uitgenodigd om deel te nemen aan een herhalingscursus in het ziekenhuis (gedurende een vijftal avonden).

Met pomp behandeling is in het begin van dit onderzoek nog weinig ervaring (1 patiënt). Verwacht wordt dat CSII een betere imitatie van de fysiologische insuline productie zal geven (zij het nog steeds op de verkeerde plaats toegediend).

In hoofdstuk 4 worden de vraagstelling en het protocol van de studie verder uitgewerkt. In een prospectief gerandomizeerd onderzoek worden 30 nieuwe kinderen met IDDM (successievelijk naar het SKZ verwezen) met hetzij CSII, hetzij conventionele injectie therapie behandeld. In beide groepen wordt semisynthetische humane insuline gebruikt. Mondelinge en schriftelijke toestemming tot deelname aan het onderzoek wordt aan ouders (en kinderen > 12 jaar) gevraagd. Gedurende 2 jaar worden de kinderen maandelijks gevolgd. In de eerste 3 maanden is de frequentie van ziekenhuisbezoeken frequenter. Na afloop van de 2 jaar worden de kinderen psychologisch getest. In dit proefschrift worden de resultaten gegeven na 1 jaar follow-up. De psychologische testen zullen dan nog niet door alle kinderen gemaakt zijn. Dit betekent dat het slechts om preliminaire gegevens zal gaan, wat betreft de psychologische testen.

Bij de diagnose IDDM wordt de mate van metabole ontregeling vastgelegd in de bloedsuiker, de bloed pH en de ketonurie. HLA typering en virusserologie zijn uitgevoerd om na te gaan in hoeverre deze samenhang vertonen met het al dan niet voorkomen van een remissie periode.

De "uitvoerbaarheid" van CSII bij nieuwe niet geselecteerde kinderen met IDDM wordt getoetst door 4 parameters:

- de acceptatie van de therapie door kind (en ouders)
- de praktische problemen (en hun gevolgen op de metabole regulatie)
- de frequentie waarmee telefonisch overleg plaatsvindt
- de frequentie van huisbezoeken door de gespecialiseerde verpleegkundige.

Als belangrijkste parameters voor de metabole controle worden maandelijks geglycosyleerd hemoglobine (sHbA1) en halfjaarlijks diverse intermediair metabolieten bepaald. De frequentie van bloedsuiker controles en het voorkomen van hypoglycaemie worden eveneens betrokken bij de metabole controle evenals de insuline dosis.

Maandelijks bepaalde C-peptide excretie in 24 uurs urine vormt de parameter voor de endogene insuline productie. De glucagon stimulatie test wordt eenmaal per half jaar uitgevoerd om eveneens informatie te verkrijgen betreffende de endogene insuline productie na stimulatie. De samenhang tussen deze twee parameters wordt beschreven. Voor de C-peptide excretie in 24 uurs urine zijn referentie intervallen berekend voor gezonde kinderen van verschillende leeftijden.

Om na te gaan in hoeverre de immunologische factoren een samenhang vertonen met de remissie periode (of een van de drie relevante factoren) zijn cytoplasmatische antistoffen tegen de eilandjes van Langerhans, complement en niet-complement bindende, en oppervlakte antistoffen tegen eilandjes van Langerhans bepaald. Insuline antilichamen zijn op 2 manieren bepaald voor de start van de therapie. Drie, 6 en 9 en 12 maanden na de ontdekking zijn ze met een methode bepaald. Tenslotte worden de statische analyses beschreven, die gehanteerd zijn om samenhang tussen de verschillende parameters aan te tonen.

Hoofdstuk 5 geeft de resultaten van het onderzoek. Van de 34 naar het SKZ verwezen kinderen zijn er 4 drop outs. Twee kinderen waren te klein voor de op dat moment beschikbare pomp (de Autosyringe AS6C, ongeveer 1 jaar later is de kleinere Eli Lilly/CPI betatron 9204 beschikbaar gekomen). Een meisje had een belaste familie anamnese voor IDDM en kreeg een pomp in plaats van de geplande CT. Een patiënte is met CT behandeld in verband met haar sociale achtergrond.

De leeftijd van de 2 groepen verschilt significant. De pompkinderen zijn ouder. Qua metabole ontregeling bij de ontdekking zijn de 2 groepen goed vergelijkbaar.

Pomp therapie bij niet geselecteerde nieuwe patiënten blijkt zeker een haalbare kaart te zijn. De acceptatie van de therapie is goed. Slechts 1 meisje heeft na 28 maanden CSII therapie te kennen gegeven op CT te willen overgaan. Praktische problemen leidend tot (ernstige) metabole ontregelingen hebben zich niet voorgedaan. De CSII groep belt minder vaak. De frequentie huisbezoeken verschilt niet tussen de 2 groepen. De resultaten van de psychologische testen betreft slechts 15 kinderen. Wat betreft de meeste aspecten lijken de 2 groepen goed vergelijkbaar. Uit een test komt duidelijk naar voren dat kinderen met CSII minder lichamelijke klachten hebben. Deze data zijn echter wel preliminair.

De metabole regulatie is, wat betreft het sHbA1, significant beter in de CSII groep. De intermediair metabolieten verschillen niet significant. Bloedsuikers worden in beide groepen ongeveer even vaak gecontroleerd. Hypoglycemieën komen niet frequenter voor in een van beide groepen. De CSII groep en CT groep gebrui-

ken vergelijkbare doses insuline. Kortom, wat de metabole regulatie betreft is alleen het sHbA1 significant verschillend.

De C-peptide excretie in 24 uurs urine in de 2 groepen is niet verschillend, evenmin als de plasma C-peptide waarden na stimulatie met glucagon. De C-peptide excretie bij de ontdekking vertoont echter een significante correlatie met C-peptide excretie na 1 jaar.

De remissie periode duurt in de CSII groep gemiddeld 4 maanden langer, een significant verschil. Geen directe associatie wordt gevonden tussen de leeftijd of de ernst van metabole ontregeling bij de ontdekking van de ziekte en de remissie periode. De immunologische factoren lijken evenmin een relatie te vertonen met de duur of het optreden van een remissie periode, echter met één uitzondering. Naast de correlatie tussen C-peptide excretie, gemeten bij de ontdekking en na 1 jaar, blijkt de aanwezigheid van insuline antilichamen voor de start van de therapie een significant negatieve correlatie te vertonen met C-peptide excretie na 1 jaar. Een eenduidige samenhang tussen de metabole instelling (sHbA1) en de endogene insuline productie (C-peptide excretie in 24 uurs urine) is niet gevonden. Wel valt het op, dat slechts eenmaal een daling van de C-peptide excretie niet voorafgegaan wordt door een stijging van het sHbA1. Een duidelijke samenhang wordt gevonden in beide groepen tussen de endogene insuline productie en de toegediende insuline tussen de 2 groepen. Alhoewel de mate van samenhang niet significant verschilt, lijkt de CSII groep een iets betere associatie te tonen.

In hoofdstuk 6 worden de verkregen resultaten vergeleken met andere studies. Bij kinderen is deze therapie tot op heden slechts in geselecteerde patiënten populaties gehanteerd. Verschillen tussen de resultaten van dit onderzoek en dat van anderen zijn de tijdskosten, de acceptatie en het voorkomen van metabole disregulaties. Ten dele kunnen deze toegeschreven worden aan het moment waarop de therapie gestart wordt. De kinderen hebben nog geen "diabetes verleden". Het is mogelijk dat de nog aanwezige endogene insuline productie eveneens een rol speelt bij het minder snel ontregelen. Bovendien moet men zich realiseren dat het om kinderen gaat. Kinderen worden mogelijk beter in de gaten gehouden door hun ouders. Dit leidt tot sneller ingrijpen bij een dreigende ontregeling.

Door een nauwkeurige follow-up van de patiënten kan in de toekomst misschien vastgesteld worden welke van deze 3 factoren de belangrijkste bijdrage levert. Het is niet goed mogelijk om de psychologische data te evalueren, doordat deze nog zeer incompleet zijn. Wel lijkt CSII zeker geen negatieve invloed uit te oefenen op de kinderen. Het belang van een intensieve educatie in het voorkomen van metabole ontregelingen is alom bekend en geaccepteerd.

Wat betreft het sHbA1 is de metabole regulatie van de CSII groep significant beter. Bij één leeftijdscategorie valt dit het meeste op, te weten bij de kleintjes van 5 jaar of jonger. Door hun leeftijdsafhankelijke problemen is het zeer moeilijk om bij hen een acceptabele metabole controle door middel van CT te

verkrijgen. Voor deze leeftijdscategorie vormt de komst van de kleine pompjes een uitkomst. Een contrast met andere studies is de relatief geringe frequentie van bloedsuiker controles. Dit gaat niet gepaard met een verhoogd optreden van hypo- of hyperglycaemie. Mogelijk speelt ook hier het moment waarop de therapie gestart is een rol.

Opvallend is de gelijke insuline dosis van de 2 groepen ondanks het verschil in sHbA1. Hierbij moet men zich echter realiseren dat insuline dosis niet hetzelfde betekent als insuline behoefte. Met name bij CT kan men niet ongestraft de insuline dosis ophogen om de metabole regulatie te verbeteren. Dit gaat gepaard met een verhoogde kans op hypoglycemieën. Een andere mogelijke verklaring voor de gelijke dosis kan gezocht worden in een verschil in insuline sensitiviteit. Hiervoor is echter verder (in vivo en in vitro) onderzoek noodzakelijk. Het volgen van de kinderen, nadat de 2 jaar van de studie voorbij zijn, is zeer interessant. Op die wijze kunnen mogelijk verdere gegevens verkregen worden over de samenhang tussen de metabole regulatie, de remissie periode en het ontstaan van chronische complicaties. Wel dient men zich te realiseren dat het om een kleine groep patiënten gaat. Suggesties voor de follow-up van deze patienten staan beschreven in hoofdstuk 6.

De endogene insuline productie is niet verschillend tussen de 2 groepen. De significante associatie tussen de endogene insuline productie bij de ontdekking en de productie na 1 jaar is eveneens in een andere studie beschreven. Het benadrukt het belang van een vroege diagnose en een vroege start met therapie.

Eveneens significant geassocieerd met de endogene insuline productie na 1 jaar is de aanwezigheid van insuline antistoffen voor de start met insuline therapie. Hun aanwezigheid leidt tot of is geassocieerd met een significant lagere C-peptide excretie na 1 jaar. Wat de rol van deze antistoffen is, is niet bekend. In hoeverre zij slechts een "marker" zijn voor beta cel destructie of actief betrokken zijn bij deze destructie dient verder onderzocht te worden.

De remissie periode duurt significant langer (4 maanden) in de CSII groep. In tegenstelling tot de retrospectieve studies is geen correlatie gevonden tussen de remissie periode en de leeftijd of de ernst van de metabole ontregeling. Deze verschillen berusten mogelijk op de verschillende definities en criteria, die gehanteerd worden bij de remissie periode. Echter, het is ook mogelijk dat een bepaalde leeftijdsgrens van belang is. Hetzelfde kan gelden voor de mate van ontregeling. De 3 kinderen, die intraveneus insuline toegediend kregen na de ontdekking vertonen geen remissie.

De overige parameters vertonen evenmin een associatie met de remissie periode.

De samenhang tussen sHbA1 en C-peptide excretie is niet eenduidig. Dat de metabole regulatie wel degelijk van belang kan zijn blijkt uit het feit, dat slechts in 1 geval een daling van de C-peptide excretie voorafgaat aan een stijging van het sHbA1. Verder onderzoek zal nodig zijn om deze samenhang te evalueren. De significante correlatie in beide groepen tussen insuline dosis

en endogene insuline productie verschilt in geringe mate. Het is verleidelijk om te suggereren dat dit verschil wijst op een verschil tussen de 2 groepen in sensitiviteit voor insuline. Men zou kunnen speculeren dat de insuline toegediend via CSII effectiever is (gezien de betere sHbA1 bij een gelijke insuline dosis). Diverse andere studies suggereren een betere insuline sensitiviteit bij CSII gebruik.

In hoofdstuk 6 worden tot slot 2 indicaties voor CSII bij nieuwe kinderen met IDDM gegeven. De al eerder genoemde categorie jonge kinderen ($\leq$ 5 jaar) vormt de eerste groep. De 2e indicatie voor CSII is nu nog niet van toepassing, maar hopelijk in de nabije toekomst wel. Indien methodes ontwikkeld zijn voor verdergaande interventie in het destructieve proces "IDDM" kan CSII als interim therapie gehanteerd worden om gedurende korte tijd de remissie periode te handhaven.

Terugkomend bij de vragen, die aan het begin van deze samenvatting geformuleerd zijn, kunnen de volgende antwoorden gegeven worden:

- CSII is toepasbaar bij niet geselecteerde nieuwe diabetes patiënten. Preliminaire resultaten van de psychologische testen suggereren geen negatieve invloed van CSII op de kinderen en hun sociale activiteiten.
- Met betrekking tot sHbA1 is de metabole regulatie in de pompgroep significant beter. De overige parameters, waaronder de insuline dosis, vertonen geen verschillen tussen de 2 groepen.
- De remissie periode duurt ongeveer 4 maanden langer in de CSII groep. Geen directe associatie is gevonden tussen het optreden van een remissie en een van de vele parameters.

De C-peptide excretie bij de ontdekking en de aanwezigheid van anti-insuline antistoffen voor de start met insuline therapie vertonen een significante correlatie met de C-peptide excretie na 1 jaar.

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CURRICULUM VITAE

De auteur van dit proefschrift werd in 1956 te Markelo geboren. Na het behalen van het diploma gymnasium bêta aan het Johan van Oldebarnevelt gymnasium te Amersfoort studeerde zij geneeskunde aan de Erasmus Universiteit te Rotterdam. Gedurende haar studie werkte zij 3 maanden als student assistent bij de afdeling Toxicologie in het Hôpital Fernand Widal (hoofd: Prof. Chantal Bismuth) te Parijs. Na het voltooien van de studie in 1982 begon zij als research fellow (mogelijk gemaakt door Sophia Stichting Wetenschappelijk Onderzoek) in het Sophia Kinderziekenhuis aan het onderzoek dat tot dit proefschrift heeft geleid. Zij was werkzaam binnen het Diabetes Team (hoofd: dr G.J. Bruining) van mei 1982 tot oktober 1985. In oktober 1985 begon zij met haar opleiding kindergeneeskunde in het Sophia Kinderziekenhuis (opleider: Prof. dr H.K.A. Visser) te Rotterdam om deze voort te zetten in april 1986 in het Hôpital d'Enfants (opleider: Prof. M. Pierson) te Nancy. De auteur van dit proefschrift is getrouwd met drs A.N. Schim van der Loeff.

LIST OF ABBREVIATIONS

CSII	Continuous subcutaneous insulin infusion
CT	Conventionally treated, Conventional Injection Therapy
HLA	Human leucocyte antigen
ICA	Islet cell antibodies
ICCA	Islet cell cytoplasmic antibodies
ICCA-CF	Complement fixing islet cell cytoplasmic antibodies
ICSA	Islet cell surface antibodies
IDDM	Insulin dependent diabetes mellitus
IgG	Immunoglobulin class G
IgGIa	Anti insulin antibodies, determined according to the method of Christiansen
IgGIb	Anti insulin antibodies, determined according to the modified more sensitive PEG method, described by Lauritzen
NEFA	Non-esterified fatty acids
RIA	Radio Immuno Assay
sHbA1	Stable glycosylated hemoglobin A1
SKZ	Sophia Kinderziekenhuis (Sophia Childrens' Hospital)
UCP	Urinary C-peptide percentage