prine and prednisolone. ATG was added to this protocol in the experimental group. The number of renal failure episodes and consequently the amount of steroid necessary to control these episodes were significantly lower in the ATG group than in the other group. Two year post-transplantation kidney survival was 79% in the ATG group and 52% in the control group.

In the second study, 15 consecutive transplant recipients were randomly assigned to two control groups and to one experimental group, where steroids were replaced by NSAI drugs. This preliminary, and very limited, pilot trial demonstrates the existence of early acute renal failure episodes, probably of immunological origin, which can improve spontaneously in the absence of steroid therapy.

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STEROIDS AND REJECTION TREATMENT IN THE GOTHENBURG TRANSPLANT PROGRAMME

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Introduction

The kidney transplant programme in Gothenburg started 15 years ago in 1965 on a modest scale during the first years, after which the frequency increased and from 1972 onwards approximately 100 kidneys per year have been transplanted. Up to now more than 1100 transplantations have been performed in 800 patients. Over 80% of the grafts have been of cadaveric origin.

Kidney transplantation has been the method of choice for the treatment of patients with terminal uraemia in our region which has resulted in only a minority of uraemic patients being taken care of by chronic dialysis. The transplantation frequency during the last 7 years has corresponded to 25 transplantations per million population per year. The acceptance of patients for transplantation has

*Unfortunately Professor Gelin was prevented by illness from taking part in this Symposium and we have since learned with sorrow of his untimely death (see Preface). Eds*
been liberal and almost all patients wanting a transplant have been included in our programme. The mean age of patients receiving cadaveric kidneys has been 44 years. Moreover, during recent years increasing numbers of high risk patients, i.e. patients older than 60 years and patients with diabetic nephropathy have been accepted. The proportion of high risk patients during the last two years has been over 25%.

In the following presentation we want to concentrate on the use of steroids in our primary cadaveric transplant programme and try to illustrate the influence of different treatment philosophies on the graft prognosis.

**Basic immunosuppression**

The basic immunosuppression during all these years has been unchanged and solely based on azathioprine and prednisolone. Very few patients have been subjected to adjunctive immunosuppression such as ALG and extracorporeal irradiation of blood.

The initial dose of prednisolone given at transplantation is 3mg/kg body weight, which is tapered down to 1mg/kg body weight at two weeks, 0.5mg/kg body weight at 6 weeks and subsequently reduced to a level of 0.2mg at one year. The total quantity of prednisolone given to a normal weight individual of 70kg will amount to 9.8g during the first year. No adjustments of the oral prednisolone have been made in rejection crises.

**Antirejection protocols and patient selection**

In the following we will concentrate on the outcome of primary cadaveric transplantation from 1969 onwards, from which period we consider the programme experienced and grown out of its infancy. The material has been divided into three periods according to the different antirejection protocols. Period I: 1969–72, a single dose of 100mg prednisolone was given together with actinomycin C, 200μg x 3–5 and local irradiation of the graft 150 rad x 3. Period II: 1973–77 methylprednisolone 1g + 0.5g + 0.5g was given for three days. The schedule was repeated up to three times giving a total amount of 6g methylprednisolone. Period III: 1978–79 the dosage of methylprednisolone was halved to 0.5g + 0.25g + 0.25g, but according to individual needs, as judged from the clinical picture, the course could be prolonged for two or more days, many times, with further reduction of the dose to 125mg. The total amount of methylprednisolone seldom exceeded 3g.

The diagnosis of rejection during periods I and II was mainly based on renal angiography while during period III it has almost exclusively been a clinical diagnosis based on daily surveillance of the patients by an experienced staff member. Moreover, methylprednisolone has been instituted on first clinical suspicion of rejection and further diagnostic confirmation has not been awaited. The donor/recipient selection principles have differed during the periods. In period I HLA-A-B-matching was the main selection principle and very few kidneys with more than one HLA-incompatibility were transplanted. In period II no regard
to HLA-matching was taken. In period III we have returned to HLA-A-B-matching but with less strict requirements than in period I, now only avoiding two HLA-B-mismatches.

During period III no patients without prior blood transfusions have been accepted for transplantation, while during period II and to a lesser degree in period I, a substantial number of the patients had not been transfused.

**Blood transfusion and HLA-matching**

Before going into the influence of different antirejection protocols for graft loss due to rejection, the effect of blood transfusions and HLA-matching on this same parameter will be briefly reported. In earlier retrospective and prospective studies we found that blood transfusions given prior to transplantation had a significant, improving influence on graft survival [1, 2]. We also found that mismatches in the HLA-B-locus negatively influenced the outcome of transplantation, as earlier reported to this association [3]. In a separate, unpublished analysis we have found that these two factors work independently of each other.

In Figure 3 we have compared transfused patients receiving kidneys with one foreign HLA-B-antigen during periods I and II and we found that during period II the graft survival was significantly better. Similar differences were also found in non-transfused patients. As blood transfusion and HLA-matching were equivalent in the two groups it seems probable that the difference depends on the

![Graph showing graft survival over time with one and two foreign HLA-B mismatches.](image)

**Figure 3.** One year primary cadaveric graft survival in pretransplant transfused patients receiving kidneys with one HLA-B mismatch. (Non-immunological causes of graft loss excluded)
different antirejection protocols. Bolus doses of methylprednisolone thus give a superior survival compared to the protocol used earlier with only modest increase of steroids.

In Figure 4 the annual irreversible rejection rate at three months is given, and no real differences between period I and period II are found, which is obviously

![Figure 4. Three months irreversible rejection rate year by year. Primary cadaveric grafts]

due to different HLA-matching principles and an increasing amount of non-transfused patients in period II. Both these factors obscure the effect of the improved antirejection therapy during the later period. During period III, however, we can see a definite decrease in the rejection rate which is slightly above 10% despite the reduction of the amount of methylprednisolone given. We ascribe this mainly to the effect of blood transfusions and elimination of unfavourable HLA-matched grafts.

During period III the frequency of acute rejections has not decreased significantly but they are mild and mostly quickly reversible. By giving lower doses of steroids during the first rejection episode we do not damage the patient and we do not drain the whole antirejection arsenal on the first rejection episode but still have an ample reserve for future rejection episodes which can be used without endangering the patient.

We have selected three representative periods within the three periods and looked at the GFR determined with Inulin or $^{51}$Cr EDTA-clearance one year after grafting. As seen in Figure 5, the one year graft survival has improved and reached 69% in 1978 and moreover 88% of these grafts have a GFR of $>40\text{ml/min}$, while very few grafts have severely impaired function. This improvement in graft function we mainly ascribed to the changed philosophy of antirejection therapy with individual treatment.
Figure 5. GFR of functioning primary cadaveric grafts at one year. Three periods with different antirejection protocols

The patient survival has increasingly improved during the years. In the last few years the one year mortality was approximately 10%, which we consider satisfactory bearing in mind that 25% of the patients are high risk patients. The improved survival is also obvious among high risk patients [4,5].

Summary

Our experience from the Gothenburg material indicates that the graft prognosis is highly dependent on pretransplant blood transfusions, to a lesser degree on avoidance of two mismatches for the HLA-B-locus and, not the least, on the use of methylprednisolone antirejection therapy. It seems that a rather moderate dosage of methylprednisolone allows us to prolong and repeat the courses according to individual needs, and this may be the main reason for the significantly improved graft function at one year. The experiences gained and the lessons learned from the transplant programme in Gothenburg have resulted in 70% of the uraemic patients in the Gothenburg region being alive with functioning renal transplants.

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Open Discussion
McGEOWN (Chairman) Thank you Dr Brynger. If I have understood you aright your graft survival has improved rather than gone down since reducing your dose of methylprednisolone by half from your original methylprednisolone protocol and I think that this demonstrates that in rejection, also, steroids have been used too liberally in the past. I understood you to say that you treated for rejection before there was a rise in serum creatinine. Is that correct and how did you then diagnose rejection?

BRYNGER That is correct. The laboratory is very slow so we had not time to await the analysis, but we go on very general clinical signs like slight fever, reduction in urinary output, and maybe a slight and general uneasiness of the patient on day seven for example. That is, if we think there might be rejection (and in a very high proportion it is a rejection) we treated. If it turns out that we are wrong we stop the course, but we say “shoot first and ask later”!

McGEOWN So you treat on suspicion?

BRYNGER Yes.

McGEOWN Which may mean that you treat some episodes that are not rejection?

BRYNGER Oh, yes, of course.

McGEOWN But obviously it is of greater importance that you have reduced your dose of steroids.

BRYNGER We don’t fear too much giving the first dosage in that situation with that philosophy.

KNAPP (Nottingham) The list of factors affecting prednisolone which Dr McGown referred to included timing. This is a new addition to the majority of lists, as most protocols state a daily dose and give no indication of when or how often the steroid or other agents have been administered. Our own research is presented on a Poster, and we have evidence that this may be an important variable which has been relatively ignored. Dr McGown’s group in Belfast have used an unusual, possibly almost unique programme, giving all their drugs at 10am. Other units in the UK, including our own, have used other programmes and have been less

1 Knapp MS, Byrom NP, Pownall R. Proc EDTA 1980; this volume
successful. I would ask that published reports state what time of day the drugs have been given, because our work in animals and humans shows that the immune response is different at different times, and our own analysis has shown that results have been different with twice daily compared with daily prednisolone and azathioprine.

McGEOWN Another point that Dr Knapp did not mention about giving the steroid in the morning is that this reproduces the normal daily variation in cortisol secretion. If it is given in this way in the morning rather than divided over the day there ought to be less pituitary/adrenal suppression and this should be even less if it is given on alternate days. Yesterday we were told that contrary to what the literature says, the use of alternate day steroids does not improve the growth rate in children but there are a number of publications which state the contrary.

KNAPP The alternate day dosage question may be an extension of the previous point in so far as when a morning only regime is used from the beginning, then alternate day therapy will be supplemented by endogenous corticosteroid production, whereas an alternate day therapy which follows a four times a day, or twice a day or evening regime will not be supplemented by endogenous production of cortisol. This may account for some of the confusion because people are getting different results from alternate day regimes because the earlier programmes of treatment were different regarding the effect of timing of prednisolone, or the dose, as a cause of adreno-pituitary suppression.

BRUNNER (Basel) Your data was an analysis of 35 cases. It was statistically significant but I am not sure that in human cadaver transplantation 35 cases can be biologically meaningful.

WOODS (Kuwait) Could Dr Crosnier tell me his rationale for Ibuprofen instead of steroids? I would sound a word of caution on two grounds, that it might increase the incidence of acute tubular necrosis and it might also increase the vascular thrombotic element of rejection.

CROSNIER I agree with what you say but this was only a trial to try to treat our patients without steroids. We are convinced that there is only a very little immunosuppressive action of steroids and that the effect of steroids is an anti-inflammatory action, so we tried this kind of anti-inflammatory drug.

CATTELL (London) What I really would like is clarification from the Gothenburg group about anti-rejection therapy. It has been our practice, like most, if we have rejection, to treat with methylprednisolone in large doses over two to three days, waiting to see by the response whether it is reversible or not. Do I understand that you are now reducing the dose but possibly continuing for more than two or three days?

BRYNGER Yes, we have a less strict three day course. After 1977 we reduced it to half, but if we don't have a good enough answer on that therapy we continue for one to three days and maybe alternate days. We might even further reduce the dosage so that we have 25mg every other day up to a total length of seven days or something like that. There is really no schedule for this. It is very individual and it depends on daily clinical bedside assessment of the patient.
HAYRY (Helsinki) After discussion on the usefulness of steroids as immuno-suppressive drugs began a few years ago, we performed a randomised trial in Helsinki. We pre-randomised the patients into two groups. The control group got a very low dose of steroids during the immediate post-transplant period, 0.4mg/kg per day or methylprednisolone in one dose. The high dose experimental group got 3.6mg/kg per day divided into three doses. When we analysed the results of these two protocols we found that with the high dose group, where we really aimed to saturate the steroid receptors, we could reduce the number of early rejections from 86% to 60%. That is not significant. However, we could delay the onset of the first inflammatory episode, monitored by fine needle aspiration cytology, from 5.4 days to 8.5 days which is significant. So we think that by having a little bit higher dose of methylprednisolone during the immediate post-transplantation period one can (a) reduce the number of early rejections, and (b) make rejection easier to overcome.

CHAN (Oxford) It seems that there is a wide variation of steroid dosage used in renal transplantation. To clarify the question as to what is the right dose of steroids to give to patients during the early period following renal transplantation, we carried out a prospective randomised trial in early 1978. The high dose group was the group that Dr McGeown has mentioned (100mg of prednisolone starting on the day after transplantation and tailing off to 20mg per day about two-and-a-half months after transplantation). The other group was the low dose group in which we started patients on 30mg of prednisolone daily for sixty days and then tapered off to 20mg daily as for the high dose group. So the high dose group will receive about double the dose of the patients in the low dose group and at the end of two-and-a-half months patients from both groups will have the same daily maintenance dose of prednisolone. There were 72 patients in this trial. There was no difference in the graft survival. At the same time we had a higher morbidity and mortality in the high dose group. Therefore we think that the high dose group should be abolished, and we are now using the low dose regime for our transplant patients.

McGEOWN Thank you Dr Chan. I am glad that you support the low dose therapy.

KOPP (Munich) If we put patients on steroid therapy for reasons other than anti-rejection in transplanted patients, for example patients with endocrine disorders or rheumatoid disorders, our endocrinologists tell us, at least for maintenance therapy, that the ideal timing of steroid therapy is 6 o’clock in the morning. I have never heard that anti-rejection therapy has ever been applied according to timing of the serological levels.

McGEOWN Yes, I think that’s right Dr Kopp. People tend to give anti-rejection therapy as soon as they think of doing it and so it is not timed, not with us either.

CAMERON (London) It seems to be fashionable! We have also been running a high dose versus low dose trial and have now entered just over 50 patients, and again we see no difference between the two. Can I be provocative, Molly, and ask you, since low doses are in fashion, whether you yourself are going to cut the fairly generous anti-rejection therapy which you add to your low dose standard background regime in view of what you have just heard?
McGEOWN We have not yet done that. I should say that our standard anti-rejection regime is 200mg of prednisolone daily by mouth for three days, reduced in three day steps to 150, 100, 75, 50 and back to 20mg a day — all by mouth. Very few patients received a single dose of 1g of methylprednisolone when we thought we had been a bit blind and not seen the rejection quickly enough. But if they seem to respond extremely quickly the oral prednisolone is reduced every two instead of three days, so we do sometimes change the regime slightly.

BARNES (Birmingham, UK) I would like to add further support to the low dose steroids. We conducted a similar trial to the ones that you have heard, but we were comparing 75mg a day tapering, against 20mg a day as a standard dose, and again there was no difference in the number of patients with surviving grafts at the end of the three month period and well beyond that time. One of the big differences was the lower rate of complications in the patients with low dosage and the mortality rate in that group was much lower. As far as the anti-rejection policies are concerned, we conducted a trial between the type of regime that Dr McGeown has just been describing and the intravenous three day 1g and again there was no difference. I think that what we do now is to use it as a matter of convenience; if the patient is actually in the hospital then we use the intravenous route and if the patient is at home then we can use the oral route quite satisfactorily.