The attenuation (or prevention) of graft rejection in renal homotransplants is attempted in various ways:

1. Surgical removal of the major lymphoid aggregations of the body, or local irradiation to render these centres incompetent.
2. Total body irradiation, in dosages just sufficient to incapacitate the host's immunologically competent cells.
3. The systemic use of cytotoxic drugs to produce a similar effect as in (2) above.
4. Prevention of graft rejection by retarding its own immunologically competent cells, either by local irradiation or as part of the systemic effect of cytotoxics. In addition, cortisone is believed to delay the release of antigen from the graft.

Currently, of the above methods, immuno-suppressive drugs appear to be the safest and most successful. Imuran is the most important of these drugs, Actinomycin C and cortisone being reserved for use as specific anti-rejection agents. It is perhaps surprising that steroids are not of greater efficacy in the reversal or prevention of repudiation.

In these experiments we attempted to assess the value of cortisone alone, infused directly by continuous intra-arterial drip into the renal artery of a transplanted kidney, in dogs. The aim, therefore, was directed at the local effect of cortisone on the graft.

MATERIAL AND METHODS

Experimental Groups

A comparison was made between 3 different groups of animals:

Group I. 12 dogs, untreated renal homotransplants.
Group II. 11 dogs, fully-treated renal homotransplants, with a conventional immuno-suppressive regime.
Group III. 7 dogs, renal homografts treated with cortisone alone by continuous intra-arterial infusion direct into the renal artery.

Surgical Technique

Adult mongrel dogs, weighing between 35 and 50 lb., were anaesthetized with intravenous pentobarbitone sodium, intubated and manually ventilated for the duration of the surgical procedure.

1. Right Nephrectomy

This is performed through a right, subcostal, muscle-splitting incision employing a non-touch technique, with meticulous dissection of the vascular pedicle. Immediately after nephrectomy, the kidney is perfused with a cold solution (5-10°C) containing low molecular weight dextran, heparin and procaine. The kidney capsule is incised and stripped along its entire length.

2. Homotransplantation

The renal artery and vein of the nephrectomized kidney are anastomosed end-to-end to common carotid artery and external jugular vein of a different animal, respectively. A muco-cutaneous ureterostomy is carefully constructed and the kidney placed deep to the panniculus carnosus in the dog’s neck. Ischaemic time averages 20-30 minutes.

3. Bilateral Nephrectomy of the Host

This is carried out simultaneously with transplantation, through a midline incision, and makes host survival entirely dependent upon the transplanted kidney.

4. Catheter Implantation

The catheter used is size PE10 polyethylene tubing, with both ends flanged by heating: the manufacturers claim that this tubing has been animal-tested and found free of tissue reaction. One end is connected to a size A Luerlock adaptor for attachment to a standard intravenous administration set.

Implantation. Various techniques were attempted but in only one could intra-arterial perfusion be continued until the animal’s death (Fig. 1).

![Fig. 1. Catheter implantation into proximal common carotid artery with end-to-end anastomosis of renal artery to distal cut end.](image-url)

As great a length as possible of common carotid artery is dissected free, proximally controlled and distally ligated, and transected. The catheter is inserted down the cut end to just above the bulldog clamp and, by tenting the artery, it is easily forced through the wall. With traction, the catheter is pulled through until the flanged end impinges against its intima. The kidney is then anastomosed to the distal end of the common carotid artery.

The thin PE10 catheter is threaded through a wider bore polythene tube and, by tunnelling deep to the panniculus, delivered through the skin at the base of the neck on the dorsum of the dog. The catheter is fixed to the skin with sutures and is then connected to the infusion.

5. Intra-arterial Infusion

As described, the catheter is connected to an intravenous infusion set by means of a Luerlock adaptor. Using an M-50 Minimeter administration set adaptor, this set is joined to another and the latter ultimately to the vacolitre containing the cytotoxic.

6. Animal Care

Modified Pavlov slings are constructed of strong canvas and adequate apertures cut for the 4 limbs, lined with foam rubber to obviate sharp, cutting edges. The dog is either suspended or allowed to stand, and is fed by hand. At night the edges of the sling are approximated to allow the animal to lie down. Transport between operating table and immobilization sling is carefully organized to assure patency of the catheter. A standard diet follows, without fluid restriction.
Cytotoxics
(a) **Group I.** No attempt was made to treat rejection.
(b) **Group II.** Fully-treated homotransplants.
   (i) *Imuran.* On the day of operation and subsequent day, 8 mg./kg. body weight is given. At the diagnosis of threatened rejection and on the subsequent day, 10 mg./kg. is given. The maintenance dose is 2 - 4 mg. kg.
   (ii) *Actinomycin C.* 200 µg. given at the time of rejection by a single intravenous injection.
   (iii) *Cortisone.* 200 mg. day from the diagnosis of rejection with a standard procedure for graded withdrawal.
(c) **Group III.** Cortisone-treated homotransplants. Cortisone is given—200 mg./day in 1 litre of ½ normal saline—by continuous intra-arterial infusion. The dose is increased depending on the clinical effect.

Investigations
The following investigations are performed daily:
(a) *Urine—*volume, protein, catalase, stained urinary sediment smear, electrolytes, urea.
(b) *Blood—*haemoglobin, white blood cell count, differential count, electrolytes, urea.
(c) *General—*graft size, pulse rate, temperature.

RESULTS
The results and details of survival times in the various groups may be seen in Table I. In groups I and II no failures occurred which were attributable to technique. The technical difficulties encountered in group III resulted from catheter implantation, including catheter blockage, haemorrhage and arterial spasm and thrombosis. In the group of 7 animals successfully perfused there were as many failures as successes.

**Group I—Untreated Homotransplants (Fig. 2)**
The results in this group are in total accord with the many detailed accounts of canine renal homotransplants published.\(^{17,20}\) Signs of threatened graft rejection became apparent 4 - 5 days after transplantation and within a further 2 - 3 days, full-blown rejection with gross impairment of renal function was evident. The increase in graft size was remarkable, in many cases becoming at least 3 - 4 times the original size (Fig. 3).

**Table I. Survival Time and Causes of Death**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of dogs</th>
<th>Onset of rejection</th>
<th>Survivors (14 days)</th>
<th>Survival time</th>
<th>Causes of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Untreated)</td>
<td>12</td>
<td>4th-5th day</td>
<td>0</td>
<td>Approx. 8 days</td>
<td>Renal failure in all</td>
</tr>
<tr>
<td>II (Fully treated)</td>
<td>11</td>
<td>5th-7th day</td>
<td>10</td>
<td>(6-11 days)</td>
<td>1 death—pneumonia</td>
</tr>
<tr>
<td>III (Cortisone only)</td>
<td>7</td>
<td>4th-5th day</td>
<td>0</td>
<td>Approx. 9 days</td>
<td>3 deaths—gastrointestinal tract haemorrhage; 4 deaths—renal failure</td>
</tr>
</tbody>
</table>

Fig. 2. Rejection at 4 days with subsequent death in uraemia at 9 days.

Histologically, there was uniformity: a massive round-cell infiltrate, gross interstitial oedema and a well-marked destruction of small vessels with fibrinoid necrosis of the vessel wall and widespread thrombosis (Fig. 4).

Fig. 3. Enormously swollen rejected kidney.

Fig. 4. Microscopy of an untreated rejected kidney. Note the gross interstitial oedema and round-cell infiltrate.
Survival time was 6-11 days, with an average of 8 days.

**Group II—Fully-treated Homotransplants (Fig. 5)**

Since none of the untreated animals survived for 14 days after transplantation, this period was taken as the survival time. Only one of the fully-treated dogs died within this period, from pneumonia. Most interesting is the fact that the kidney of this non-survivor was within the range of normality, both micro- and macroscopically.

Little difficulty was experienced with the reversal of threatened homograft rejection. The dangers resulted from the use of cytotoxics, with their attendant complications, the most common being liability to infection. It should be noted that cortisone was used in this group specifically as an anti-rejection agent, in combination with other drugs.

**Group III—Cortisone-treated Homotransplants (Fig. 6)**

There was a striking similarity in the results of groups I and III. The diagnostic criteria of homograft rejection appeared at the same stage and there was no significant difference in survival time. All the animals in group III died within 14 days. Unlike group II, threatened rejection could neither be delayed nor reversed. Increasing the dosage of cortisone did not discernably alter the picture of renal failure resulting from rejection.

Increase in graft size in group III, although apparent, was never as gross as in group I. The significance of this is not understood. The diagnostic abnormal urinary sediment constituents were identical in groups I and III, both quantitatively and qualitatively.

In group I dogs an eosinophilia was always apparent on examination of a peripheral blood smear. In neither of the other two groups was this noted and, in fact, in group III an eosinopenia was associated with a peripheral lymphopenia.

Immuno-suppressive drugs depend largely upon depression of the white cell series and antibody formation, thereby increasing liability to infection. In group III, although infection was not a real problem, massive gastrointestinal tract haemorrhage accounted for 3 deaths in 7 animals; this is a well-documented side-effect of steroid therapy, and typical ulceration was found at postmortem examination.

Both macro- and microscopically, all the recognized pathological features of homograft rejection were present in group III, but to a lesser extent as in untreated group I animals. The most obvious differences lay in the reduction in interstitial round-cell infiltrate, and a less marked vascular endothelial reaction.

**DISCUSSION**

Many attempts to prevent or reverse canine renal homograft rejection by the use of corticosteroids alone have been reported. In such experiments, drug administration invariably has been parenteral.

By direct intra-arterial infusion into the renal artery of a transplanted kidney, not only was maximal dosage assured but this dosage could be sustained continuously for the duration of the experiment. Using this technique, it was felt that the effects of this drug on the graft could be gauged. Without clearing the renal venous return of steroid, the systemic effect was also still operative; however, the aim was that the local effect should predominate.

It is reasonable to expect a modification of the rejection reaction by corticosteroids when the possible modes of action are considered.

1. Steroids inhibit the synthesis of various antibodies. This applies to circulating antibodies to purified antigens, and it is unlikely that it has any application to tissue immunity responses.

2. Steroids decimate the lymphocyte population, attributed to its involving action on lymph nodes. The lympholytic action may be similar to that of antimetabolites, since both drugs appear to block the inductive phase of antibody formation.

3. Steroids delay the release of antigens from the homograft. This postulate is based on the work of Billingham, Kron and Medawar, in which cortisone prolonged the survival of rabbit skin homografts. The resultant associated diminished vascularity and reticulo-endothelial depression cannot be ignored. It has recently been shown that more potent synthetic
corticosteroids, like triamcinolone, prevent experimental glomerulonephritis. As the glomerular basement membrane is antigenic, it is possibly the first area to be damaged in the transplanted kidney.

4. Steroids delay vascularization. This does not apply to organs transplanted with direct arterial anastomosis.

5. Steroids delay the onset of the inflammatory responses. This suggests a peripheral level of action which, although it exists, is probably trivial.

The effect of adrenal cortical extracts on the mitigation of the homograft rejection process has been studied extensively. The findings of Billingham and his associates, and of Morgan, show that cortisone prolongs the life of skin homografts. This has been confirmed by others. However, with less rigidly controlled experimental conditions than those of Billingham, the effect of steroid therapy on homograft survival has been difficult to demonstrate. Most studies suggest that steroid therapy in large doses modifies rejection slightly, but that the effect is of little clinical value. A notable exception is the work of Mitchell et al., who used a new and more potent corticosteroid, triamcinolone, which significantly prolonged renal homografts in sheep. Using very small amounts, animals survived for 36-38 days, whereas without treatment the survival time was 3-6 days.

In these experiments accurate assessment of the local or peripheral effects of cortisone on a homografted kidney was made. It was imperative, therefore, to submit the homograft to adequate dosage, and 200 mg. per day was administered—a dose efficiently clinically as an anti-rejection agent.

With so many possible modes of steroid activity in modifying the rejection phenomenon, and in particular those of so-called peripheral importance, it was disappointing that so little was achieved in improving function or survival time—particularly as the systemic effect was not diminished. Furthermore, when clear signs of rejection were present, increasing the dosage did not noticeably improve or reverse these features.

The correlation of function and survival with the histological presentation was difficult to interpret. All the features of rejection were present but, compared with the kidneys of the untreated group, were much less severe. This observation has been noted by others but no satisfactory explanation has been forthcoming, either in other reports or as a result of our work.

Isolated reports suggest that steroids may be more valuable when used in combination with other agents. Baker et al. concluded that the combination of nitrogen mustard and cortisone has a better effect on graft survival than either agent alone.

With such poor results from the use of cortisone as a single drug, our study in fact focuses attention on its use as supplementary therapy in animals receiving continuous treatment with more powerful agents. If basic therapy is provided with Imuran, as in our group of fully-treated animals, the steroids can be withheld until the onset of rejection. Then, administered with Actinomycin C, rejection may be completely reversed with ease.

CONCLUSIONS

1. The technique of continuous intra-arterial direct infusion into the renal artery of a homotransplanted kidney is difficult but can be achieved.

2. With this technique, cortisone alone in high dosage did not significantly improve functional capacity of canine homotransplant kidneys, or their survival time, although modifying the pathological processes.

3. There is doubt as to the local or peripheral action of cortisone on the homografted organ itself.

4. In conjunction with other drugs, cortisone apparently has some value as a specific anti-rejection agent.

We wish to thank Prof. J. H. Louw, Head of the Department of Surgery at the University of Cape Town, for his continuous enthusiasm and encouragement; Dr. M. S. Barnard and Mrs. I. du Toit, for technical assistance; and Mr. G. McManus, for the photography. Acknowledgements are due to the University of Cape Town J. S. Malais Surgical Research Fund and staff research grants for financial support.

REFERENCES

The above ambitious title represents an attempt to assail a very difficult and worrying problem. Medical decisions have to be taken at 2 stages in the management of psychiatric patients charged with antisocial behaviour: (a) before, at or after trial; and (b) after the patient has been declared not responsible.

Differences of opinion are given much publicity and bring psychiatry into disrepute. This again reflects on the patient and aggravates his isolation and rejection by society and the professions. This rejection is related to the patient's failure to fulfill the role assigned to a sick person in our culture. This failure as well as his disturbed behaviour are both integral parts of his basic disability for which he cannot be blamed.

The material forming the basis of this study comes from the second stage of our medical management of these cases. At this stage members of the medical profession have testified to the effect that the patient is not responsible, thus the onus is on the profession to declare the patient fit to return to society with due regard to possible risk to other members of society.

The records of 1,913 State President's Decision (SPD) patients and 106 criminal patients have been studied during 1964-1965. SPD patients have been declared not responsible by a court of law, and criminal patients have been convicted of a criminal offence and transferred to a mental hospital subsequently because of a diagnosis of mental illness.

The classification of mental illness is notoriously difficult because of the fact that we do not understand essential mechanisms in the causation of the functional psychoses. This study is based on facts related to the case material and uses current concepts of mental disease, inadequate though they are.

The race and sex distribution of the patients are given in Table I, which also shows the influence of cultural and socio-economic factors on the incidence of behaviour disturbance associated with mental disease, as seen in the mental hospital under sections 30 and 34 of chapter II of the Mental Disorders Act. The Coloured and Bantu rates are high, followed by the Whites. The Asian figure is very low despite the half million Asian inhabitants of the Republic (mainly of Indian origin). Two possible explanations come to mind: (a) the relatively efficient Indian family as a sociological unit—victims of mental disease are protected by relatives better than in other races; and (b) Indians are less prone to commit the crimes of violence which predominate in this series.

Males predominate in all races, but it seems that the White female is relatively better shielded from the consequences of mental illness with regard to behaviour disturbances and clashes with the law.

The proportions of total patients in our psychiatric hospitals are interesting and tend to support previous submissions that the incidence of crime is directly statistically correlated with facilities provided for mental illness.\(^1\)

The average age on admission for all races was the early 30s, but the ages of non-White patients have often to be estimated. Only about one-fifth of all the cases were married, which reflects basic maladjustment in the patients comprising the series.

\section*{Type of Crime}

There are differences in type of crime and diagnosis in the different races. In the Whites 41\% committed crimes of violence, against 58\% Coloured and 69\% Bantu. This is again related to relative adequacy of treatment facilities for psychiatric invalids.\(^1,2\) The predominant diagnosis in non-Whites is schizophrenia. Defective mental development (DMD) dominates the scene in the Whites. In the Whites 87\% were high-grade defectives, as compared to 79\% in the Coloured group and 57\% in the Bantu.