# Therapeutic Review

# Cyclosporin A: a powerful immunosuppressant

A. LAUPACIS, MD
P.A. KEOWN, MB, CH B, FRCP[C]
R.A. ULAN, MD, FRCP[C]
N. MCKENZIE, MB, CH B, MD, FRCS[C]
C.R. STILLER, MD, FRCP[C]

**Cyclosporin A (CyA) is a powerful immunosuppressive agent whose lack of myelotoxicity makes it unique among nonsteroidal drugs currently given for immunosuppression. It has been used with initial success in recipients of kidney, liver, bone marrow and pancreas transplants, and it may also have clinical application in the treatment of autoimmune disorders. In regard to its use in transplant recipients, there are many remaining questions about its mechanism of action, the optimum dose, whether it should be used alone or with other immunosuppressants, whether it can suppress chronic rejection and what its long-term side effects may be. These questions can only be answered by further careful laboratory investigation and controlled clinical trials. Until then, CyA should only be administered in centres experienced in its use.**

**La cyclosporine A (CyA) est un immunosuppresseur puissant dépourvu de myélotoxicité, ce qui le rend unique parmi les médicaments non stéroïdiens couramment administrés pour fin d'immunosuppression. Elle a été utilisée avec un succès initial chez des receveurs de greffes rénales, hépatiques, myéloïdes ou pancréatiques, et elle pourrait également trouver une application clinique dans le traitement des maladies auto-immunes. En ce qui concerne son utilisation dans les greffes, il reste encore plusieurs questions à élucider à savoir son mécanisme d'action, sa dose optimum, si elle doit être administrée seule ou associée à d'autres immunosuppresseurs, si elle peut maîtriser un rejet chronique et quelles sont ses réactions adverses à longue échéance. Seuls des études de laboratoire méticuleuses et des essais cliniques contrôlés pourront trouver réponse à ces questions. D'ici là, l'administration de la CyA doit être réservée aux centres possédant de l'expérience dans son emploi.**

From the nephrology and transplant unit, department of medicine, University Hospital, University of Western Ontario, London

Reprint requests to: Dr. C.R. Stiller, Chief, Nephrology and transplant unit, University Hospital, 339 Windermere Rd., London, Ont. N6A 5A5

Cyclosporin A (CyA) was discovered by Borel at Sandoz Laboratories in 1972. Subsequent investigation has shown it to be the first of a new class of powerful and relatively selective immunosuppressive agents. Preliminary studies in animals and humans, pioneered by Calne, indicate that it will likely become extremely useful in the prevention of transplant rejection and may also prove valuable in the treatment of some autoimmune diseases. This review will discuss CyA's mechanism of action, its early clinical use and its possible future applications.

## Structure and metabolism

CyA is a cyclic endecapeptide (Fig. 1), of molecular weight 1202.6, obtained from the fermentation broth of two fungi, *Trichoderma polysporum* and *Cylindrocarpon lucidum*.[1] It is available for both oral and parenteral use. CyA is extremely lipophilic and therefore does not dissolve readily in standard intravenous preparations; however, Sandoz has produced an intravenous preparation of CyA that contains cremophor as the solubilizing agent. We prefer to use the oral route whenever possible, reserving the intravenous route for patients unable to take medication by mouth.

When CyA is taken orally by a human its serum concentration rises rapidly, reaching a peak at approximately 4 hours, and, with a half-life of 4 hours,

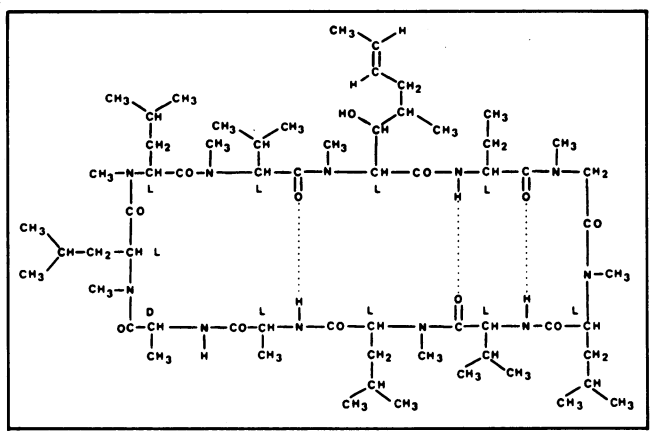

**FIG. 1—Molecular structure of cyclosporin A (CyA).**

decreases to a basal level at 12 to 24 hours.[2] Although satisfactory serum levels of CyA can be attained with intramuscular injection, the drug's absorption from muscle is unreliable. Preliminary data suggest that CyA is extensively metabolized in the liver[3] and that the metabolites are less immunologically active than the parent molecule (J.F. Borel: personal communication, 1981).

A radioimmunoassay to measure CyA levels in the serum is available. Therefore, the CyA dose can be adjusted in individual patients.[2] We aim for a trough serum level of 100 to 400 ng/ml and a level 2 hours after the dose is ingested of 400 to 1000 ng/ml after observing that CyA had little immunosuppressive effect in mixed lymphocyte culture at concentrations of less than 100 ng/ml, and that it often had nephrotoxic and hepatotoxic effects when its trough serum level was above 400 ng/ml. Our subsequent experience has supported these impressions, but more investigation is needed to conclusively establish the therapeutic range of serum levels. We have found that the dose of CyA required to maintain a trough level of 100 to 400 ng/ml decreases markedly after renal transplantation and varies considerably between patients. This does not appear to be due to a change in the drug's half-life but may be due to a change in its volume of distribution in the body (unpublished data).

**Mechanism of action**

Fig. 2 depicts a simplified version of the immune response to an allograft, divided into induction, regulation and destruction (effector) phases. During induction the foreign antigens borne on the graft trigger the proliferation of bone marrow-derived (B) lymphocytes, which evolve into antibody-producing plasma cells, and thymus-derived (T) lymphocytes, which develop into helper, suppressor and killer cells. The helper and suppressor cells regulate the immune response by enhancing or suppressing the B- and T-cell responses. The effector phase in humans consists of humoral and cell-mediated responses, which can be assessed by measuring lymphocyte-mediated cytotoxicity, complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. In the transplant patient these types of cytotoxicity can be measured through the use of donor spleen cells labelled with chromium 51 as target cells.[2]

There is still some uncertainty about the site at which CyA exerts its effect. In their initial studies of the drug, Borel and his colleagues[1] found that CyA inhibited a number of T-cell-dependent functions, such as graft-versus-host disease (GVHD), allergic encephalomyelitis, Freund's adjuvant arthritis and tuberculin hypersensitivity, but had no effect on B-cell responses to the B-cell mitogen lipopolysaccharide. It is presently felt that CyA selectively inhibits the clonal proliferation of helper T-cells, thereby preventing the three types of cytotoxicity mentioned. It has less effect on suppressor T-cells and thus creates an imbalance in the interplay between helper and suppressor cells in favour of the latter, so that the immune response is muted.[4,5] There are also isolated reports that CyA inhibits natural killer cells[6] and memory T-lymphocytes.[7] CyA appears to be more effective when administered early in the induction phase of an immune response, when the T-cells are replicating, but is inactive against mature killer cells.

CyA is an extremely powerful immunosuppressant. It has allowed successful allogeneic organ transplantation in many species (including mice, rats, rabbits, dogs, pigs, monkeys and humans), some of which had previously been notoriously resistant to transplantation.[8-14] The organs that have been transplanted, many across major histocompatibility barriers, include liver, kidney, heart, pancreas, bone marrow, nerve, cornea, skin and lung. In general the side effects have been few and minor, but graft survival and function have varied, depending upon the species and the type of graft.

It is not clear whether CyA's inhibition of helper T-cells is specific for one clone of cells responding to a single antigen, or if it is a more generalized and nonspecific immunosuppression. This is important clinically, because generalized immunosuppression would be expected to predispose the patient to neoplasia and infection, whereas a specific inhibition would not. An initial finding that caused a great deal of excitement was the discovery that certain animals tolerate grafts for long periods after a short (7- to 14-day) initial course of CyA, with no subsequent immunosuppression.[14] This led to the hypothesis that CyA permanently eliminates the clone(s) of cells reactive against the allograft. However, this is no longer felt to be true because most of these grafts show some evidence of rejection. Deeg and associates[9] demonstrated conclusively that dogs consistently reject skin grafts shortly after CyA therapy is stopped, and that the rejection process is reversed by the resumption of therapy. In humans it seems that continuous administration of CyA is needed to prevent the rejection of grafted solid organs.[15] However, in certain recipients of bone marrow transplants who show no evidence of GVHD after 4 to 6 months, Powles and colleagues[16] have been able to withdraw CyA therapy completely, with good clinical results after a median follow-up period of 7 months (longest period 13 months).

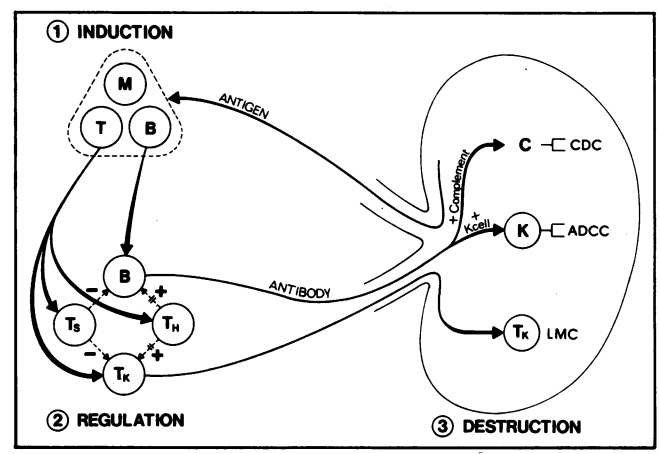


**FIG. 2—Immune response to allograft. M = macrophage; T = T-cell; B = B-cell; $T_S$ = suppressor T-cell; $T_H$ = helper T-cell; $T_K$ = killer T-cell; C = complement; CDC = complement-dependent cytotoxicity; K = K-cell; ADCC = antibody-dependent cell-mediated cytotoxicity; LMC = lymphocyte-mediated cytotoxicity. CyA is thought to selectively inhibit helper T-cells.**

**Use in human recipients of transplants**

Although there are no reports of controlled prospective clinical trials comparing CyA with conventional methods of immunosuppression, there is now considerable reported experience in the use of CyA in human recipients of kidney, liver, bone marrow and pancreas transplants (Table I). All the groups have their own protocols for dose, frequency, time and route of administration, and concomitant use of other immunosuppressive agents. It will be some time before an optimum regimen is established for each organ transplanted.

Calne and coworkers[17] used CyA initially as the only immunosuppressive agent, in a daily dose of 10 to 25 mg/kg, for 51 renal allograft recipients. They gave it intramuscularly for the first 2 to 3 postoperative days, and then orally, reducing the dose by 2 mg/kg each month starting at 2 weeks, to achieve a maintenance daily dose of 6 to 8 mg/kg. Therapy was switched to azathioprine and prednisolone if the patient experienced frequent early rejections. Of the 51 patients 13 had good graft function with CyA therapy alone and did not receive steroids; a further 29 received steroids but did not require long-term maintenance steroid therapy for maintenance of their grafts.

Starzl and collaborators[18] used CyA in an initial dose of 17.5 mg/kg taken orally once a day for 37 recipients of cadaveric renal transplants. The dose was decreased 2 months after transplantation or earlier if nephrotoxic effects were suspected. After a follow-up period of 1 to 6.5 months 89% of the grafts were functioning. Two patients died from conditions unrelated to their immunosuppression. Two grafts were rejected in patients whose first transplants, received 6 and 18 months previously, had been rejected, and a third graft was removed because of ureteral necrosis. Although the follow-up period was short, the rate of graft survival with CyA therapy is impressive.

Sweny and associates[19] treated 19 renal transplant recipients with CyA, using three regimens: (a) CyA alone (15 to 30 mg/kg a day); (b) CyA (25 mg/kg a day), azathioprine (1.5 mg/kg a day) and prednisolone; and (c) CyA alone (17 mg/kg a day) after diuresis was established. The serum levels of CyA were not measured, and the doses were kept constant. Although the follow-up periods are not indicated in the report, only 9 of the 19 patients had functioning grafts when it was written. Five patients (four in the group treated with regimen b) had severe infections, two of them fatal. In one patient receiving CyA alone a B-cell lymphoma developed 6 months after transplantation. In seven patients a switch to conventional therapy resulted in a dramatic fall in the serum creatinine level, which suggests that CyA may have had nephrotoxic effects in these patients.

Table I—Experience with CyA in human recipients of organ transplants

| Organ and investigators | No. of transplants | | Longest survival (mo)* |
|---|---|---|---|
| | Total | Functioning* | |
| **Kidney** | | | |
| Calne et al[17] | 51† | 36 | 24 |
| Starzl et al[18] | 37 | 32 | 6.5 |
| Sweny et al[19] | 19 | 9 | NR |
| Stiller et al[20] | 16 | 13 | 16 |
| **Liver** | | | |
| Starzl et al[21] | 14 | 10 | 14.5 |
| Calne et al[17] | 6‡ | 4 | NR |
| **Bone marrow** | | | |
| Powles et al[16] | 20 | 13 | 13 |
| Gluckman et al[22] | 13 | 6 | 18 |
| **Pancreas** | | | |
| McMaster et al[23] | 9§ | 5 | 11 |

*At time of report; NR = not reported.
†Six of whom received a pancreatic graft simultaneously.
‡One of whom received a pancreatic graft simultaneously.
§Six of whom received a renal graft and one a liver graft simultaneously.

At present it is not known whether CyA is best given alone or with steroids. Of the first 14 patients that Calne and coworkers[17] treated with CyA, 6 died of sepsis, and lymphomas developed in 3. Many of these patients had received steroids in high doses and cytimun, a cyclophosphamide derivative. Calne and coworkers felt that these complications were due to excessive immunosuppression, so they began giving CyA alone as the initial immunosuppressant. They do use steroids to treat rejection episodes but attempt to discontinue them as soon as possible. With this regimen graft function has been good and the incidence of infection relatively low. In contrast, Starzl and collaborators[18] found that steroids were an essential adjunct to CyA therapy. They used, usually with dramatic success, short bursts of high-dose intravenous or oral steroid therapy if rejection was suspected in the first few days after transplantation. They also noted a gradual but progressive impairment of renal function a few weeks after transplantation in some patients receiving CyA alone. This could often be reversed by adding low-dose oral therapy with prednisone (10 to 20 mg/d) or decreasing the dose of CyA or both. They concluded that, for optimum immunosuppression, steroids should be used in addition to CyA, although the dose required was much lower than that formerly needed with azathioprine. The question of whether CyA is best given alone or with steroids is still unresolved and may only be answered by a randomized trial.

Of the 16 patients in our centre treated with CyA as part of a pilot study 13 recipients of cadaveric renal transplants were given CyA orally immediately after transplantation (20 mg/kg a day, given every 12 hours). A small nasogastric tube was inserted if nausea was a problem. Initially steroids were given for maintenance therapy, and throughout the study no other immunosuppressive agent was routinely given during the first 14 days after transplantation unless there was an acute rejection, in which case methylprednisolone (250 to 1000 mg/d) was given intravenously for 3 to 5 days. On day 14 alternate-day therapy with prednisone was started in most patients with a dose of 1 mg/kg; the dose was reduced by 5 mg every other day if clinical conditions allowed, until the patient was receiving approximately 0.3 mg/kg every other day. At 3 months, if there was no evidence of rejection, the dose was lowered to 0.25 mg/kg every other day. At the time of writing, none of the 13 recipients of cadaveric transplants have died and 10 still have functioning grafts. Two grafts underwent acute rejection and a third chronic rejection. From this experience our initial

impression is that CyA provides good immunosuppression in the early post-transplantation period, with few side effects, provided that its serum levels are controlled.[20]

We are presently involved with the Canadian Multicentre Transplant Study Group in a randomized controlled clinical trial comparing the efficacy of CyA and conventional therapy in recipients of cadaveric renal transplants. The other participating centres are in Vancouver, Edmonton, Calgary, Winnipeg, Hamilton, Toronto, Montreal and Halifax. The patients are receiving CyA according to the protocol of our pilot study. Blood samples are drawn frequently (sometimes daily) during the first 3 to 4 weeks after transplantation for measurement of the drug's serum level, and the dose is adjusted as rapidly as possible to achieve a serum trough level of 100 to 400 ng/ml. The patients allocated to conventional therapy are given the best therapy available locally; this varies among the centres but always includes the use of azathioprine and prednisone. A minimum of 100 patients will be entered in each of the therapy groups, and renal function and complications will be monitored for 5 years after transplantation.

Starzl and collaborators[21] used CyA in 14 recipients of liver transplants, 10 of whose grafts were functioning after 8 to 14 months. These results were markedly superior to those achieved by this group with conventional therapy. There were two operative deaths, one due to hemorrhage and the second to an inability to close the abdominal wall because the graft was too large. Calne and coworkers[17] reported using CyA in six recipients of liver transplants, four of whom were alive at the time of the report. In one case, therapy was switched to azathioprine and prednisolone soon after transplantation.

Powles and colleagues[16] used CyA to prevent GVHD in 20 patients receiving allogeneic bone marrow transplants. CyA was given intramuscularly in a daily dose of 25 mg/kg for the first 5 days, and then orally in a daily dose of 12.5 mg/kg for 4 to 6 months. Only 1 of the 20 patients died of acute GVHD, compared with 11 of the 26 patients treated previously with methotrexate at the same institution. At the time of reporting, 13 patients were alive and well (the longest survival time was 56 weeks). In light of this experience it seems that CyA is a promising agent for the prevention of GVHD. Unfortunately, it was of no use in abolishing established GVHD. Gluckman and coworkers[22] used CyA in 13 recipients of bone marrow transplants, 6 of whom were still alive after 60 to 220 days. Many renal and hepatic complications, including anuria, the hemolytic–uremic syndrome, hyperbilirubinemia and an elevated serum alkaline phosphatase level, developed that were attributed to CyA toxicity. The CyA serum levels were not measured.

McMaster and associates[23] used CyA alone in nine recipients of pancreatic transplants. One patient died of congestive heart failure. Thrombosis of the graft occurred in two patients, and secondary hemorrhage into the pancreas, necessitating its removal 5 weeks after transplantation, occurred in another patient.

Heart and heart/lung transplants have been done with CyA therapy, but the data have not yet been published.

## Other clinical uses

CyA has been used in small numbers of patients with conditions that may be immunologically mediated.

Routhier and colleagues[24] gave six patients with primary biliary cirrhosis 5 to 10 mg/kg of CyA daily for 8 weeks. Their serum aspartate aminotransferase and alkaline phosphatase levels fell significantly. The serum levels of CyA were not measured, and the drug was discontinued because of mild rises in the serum creatinine and blood urea nitrogen levels. No follow-up findings were reported.

Mueller and Herrmann[25] used CyA in four patients with severe psoriasis and found that the skin lesions regressed dramatically approximately 1 week after the start of CyA therapy but reappeared when the drug was discontinued.

Five patients with systemic lupus erythematosus were treated with CyA by Isenberg and coworkers.[26] The arthralgia of two lessened, but the other patients found no change in their symptoms. The drug was discontinued in all five patients because of side effects (nausea, vomiting, paresthesia, nephrotoxic effects and angioedema). The serum levels of CyA were not monitored.

The incidence of side effects in these series of patients is higher than one would expect from the experience with CyA in transplant recipients and suggests the need for careful regulation of the drug's serum levels.

## Side effects

In general CyA has had relatively little toxicity when employed alone, especially as clinicians have become more experienced with its use. One of its major advantages compared with conventional immunosuppressives is its lack of myelotoxicity: no episodes of bone marrow suppression due to CyA have yet been described. This is especially significant for bone marrow transplantation, as one does not wish to suppress the newly transplanted marrow.

Nephrotoxic effects, both acute and chronic, are among the most common side effects of CyA therapy.[15] We feel that both types are usually associated with high serum levels of CyA and can be reversed by lowering the dose to achieve a therapeutic serum level.[24-27] However, we have had one patient with a gradually rising serum creatinine level who showed no evidence of rejection and whose serum levels of CyA were within the therapeutic range. When CyA was replaced with azathioprine his creatinine level fell immediately. We have interpreted this as an instance of a nephrotoxic reaction to CyA, possibly due to abnormal sensitivity to the drug or due to the accumulation of nephrotoxic metabolites.

The renal biopsy findings in patients for whom CyA is nephrotoxic may be normal, but they are often indistinguishable from those of mild chronic rejection.[28] Mihatsch and collaborators[29] have reported giant mito-

chondria in the renal tubular cells of patients receiving CyA who had clinical evidence of a nephrotoxic reaction. However, this finding can also be made in renal transplant patients not receiving CyA. In renal biopsy specimens from three recipients of bone marrow transplants who were thought to have a CyA nephrotoxic reaction Shulman and associates[30] described glomerular-capillary thromboses, mesangial sclerosis and severe tubulointerstitial disease. Although these findings are nonspecific, they were not present in other patients not treated with CyA, so they suggest that CyA may be associated with renal endothelial damage leading to microvascular thromboses. It is hoped that with more experience biopsy changes specifically due to CyA toxicity will be recognized.

We must emphasize that nephrotoxic effects are seen in only a minority of patients; most patients are able to take the drug for long periods without renal impairment. It is not always clear whether a slow rise in the serum creatinine level following renal transplantation is due to chronic rejection or a toxic reaction to CyA, which require different forms of therapy. We have found that the resolution of this question is greatly aided by measurement of both the serum level of CyA and the immune response to donor tissue, as judged by the lymphocyte-mediated and complement-dependent cytotoxicity.[2] If there is minimal or no interstitial cellular infiltrate in the biopsy specimen, the serum level of CyA is high, and tests for both types of cytotoxicity give negative results, a toxic reaction to CyA is the most likely diagnosis. Chronic rejection is suggested by a cellular infiltrate with vascular abnormalities (intimal proliferation and degenerative changes) in the biopsy specimen, a normal or low serum level of CyA and laboratory evidence of lymphocyte-mediated or complement-dependent cytotoxicity. In the first situation we decrease the CyA dose, and in the second we give methylprednisolone intravenously and increase the CyA dose if the serum level is low.

The hepatotoxic effects of CyA are dose-dependent and manifest by readily reversible rises in the serum levels of bilirubin, liver enzymes and alkaline phosphatase.[18] Clinical effects of hepatotoxicity are rarely seen when the serum concentration of CyA is at a therapeutic level, and have not prevented the successful use of CyA in recipients of liver transplants.

Other occasional side effects include a mild tremor, neuropathy, gingival hypertrophy and hirsutism. The last can be severe and embarrassing, but is reversible with discontinuation of the drug. It is our initial impression that these patients may be more susceptible to the dermatologic side effects of prednisone, such as acne, than are patients treated with azathioprine.

The relative incidence of infection during CyA therapy as compared with conventional therapy is not clear. Most authors, ourselves included, feel that life-threatening bacterial infections are less frequent with CyA therapy, but Sweny and associates[19] have found the opposite to be the case. Controlled clinical trials are needed to resolve this issue.

Thiru and colleagues[31] reported the development of lymphomas in 3 of 57 patients 4 to 11 months after the start of CyA therapy. All three patients had been given higher doses of CyA than are presently used, and all showed a rise in the titre of antibody in their serum to the capsid antigen of the Epstein–Barr virus (EBV). Crawford and coworkers[32] have shown that patients receiving CyA cannot mount a cytotoxic response to EBV-infected cells in vitro. The tumours in Thiru and colleagues' patients likely developed as a result of an impairment in T-cell function that led to decreased immunologic surveillance and permitted polyclonal proliferation of B-cells and the transformation of an EBV infection into an unlimited lymphoproliferative process. Altogether only four lymphomas have been reported in 450 patients receiving CyA, an incidence no higher than that seen in transplant patients given other immunosuppressive agents. CyA is not mutagenic in the Ames test[31] and has not been shown to produce chromosomal abnormalities. Indeed, the fact that the lymphomas occurred in the early post-transplantation period suggests that CyA allowed another agent, such as EBV, to express its oncogenicity. Longer follow-up is needed before the true incidence of lymphomas in patients receiving CyA is known.

Our work is supported in part by grants from the Medical Research Council of Canada, the Richard and Jean Ivy Fund and the Sandoz Corporation. Dr. Laupacis is an MRC fellow.

## References

1. BOREL JF, FEURER C, MAGNÉE C, STÄHELIN H: Effects of the new anti-lymphocytic peptide cyclosporin A in animals. *Immunology* 1977; 32: 1017–1025

2. KEOWN PA, STILLER CR, ULAN RA, SINCLAIR NR, WALL WJ, CARRUTHERS G, HOWSON W: Immunological and pharmacological monitoring in the clinical use of cyclosporin A. *Lancet* 1981; 1: 686–692

3. BEVERIDGE T, GRATWOHL A, MICHOT F, NIEDERBERGER W, NEUSCH E, NUSSBAUMER K, SCHAUB P, SPECK B: Cyclosporin-A: pharmacokinetics after a single dose in man and serum levels after multiple dosing in recipients of allogeneic bone-marrow grafts. *Curr Ther Res* 1981; 30: 5–18

4. TUTSCHKA PJ, BESCHORNER WE, ALLISON AC, BURNS WH, SANTOS GW: Use of cyclosporin A in allogeneic bone marrow transplantation in the rat. *Nature* 1979; 280: 148–151

5. LEAPMAN SB, FILO RS, SMITH EJ, SMITH PG: In vitro effects of cyclosporin A on lymphocyte subpopulations. 1. Suppressor cell sparing by cyclosporin A. *Transplantation* 1980; 30: 404–408

6. INTRONA M, ALLAVENA P, SPREAFICO F, MANTOVANI A: Inhibition of human natural killer activity by cyclosporin A. *Transplantation* 1981; 31: 113–116

7. LEAPMAN SB, FILO RS, SMITH EJ, SMITH PG: Differential effects of cyclosporin-A on lymphocyte subpopulations. *Transplant Proc* 1981; 13: 405–409

8. GREEN CJ: Immunosuppression with cyclosporin A: a review. *Diagn Histopathol* 1981; 4: 157–174

9. DEEG HJ, STORB R, GERHARD-MILLER L, SHULMAN HM, WEIDEN PL, THOMAS ED: Cyclosporin A, a powerful immunosuppressant in vivo and in vitro in the dog, fails to induce tolerance. *Transplantation* 1980; 29: 230–235

10. HOMAN WP, FRENCH ME, MILLARD PR, MORRIS PJ: A study of eleven drug regimens using cyclosporin-A to suppress renal allograft rejection in the dog. *Transplant Proc* 1981; 13: 397–401

11. HOMAN WP, FRENCH ME, MILLARD P, DENTON TG, FABRE JW, MORRIS PJ: Studies on the effects of cyclosporin A upon renal allograft rejection in the dog. *Surgery* 1980; 88: 168–173

12. WHITE DJ, TIMMERMAN W, DAVIES HS, NAGAO T, KASAHARA K, PLUMB A: Properties of cyclosporin-A-induced graft acceptance. *Transplant Proc* 1981; 13: 379–382

13. GRATWOHL A, FORSTER I, SPECK B: Skin grafts in rabbits with cyclosporin A. Absence of induction of tolerance and untoward side effects. *Transplantation* 1981; 31: 136–138

14. HOMAN WP, FABRE JW, WILLIAMS KA, MILLARD PTR, MORRIS PJ: Studies on the immunosuppressive properties of cyclosporin A in rats receiving renal allografts. *Transplantation* 1980; 29: 361–366

15. KLINTMALM GBG, IWATSUKI S, STARZL TE: Nephrotoxicity of cyclosporin A in liver and kidney transplant patients. *Lancet* 1981; 1: 460–471

16. POWLES RL, CLINK HM, SPENCE D, MORGENSTERN G, WATSON JG, SELBY PJ, WOODS M, BARRETT A, JAMESON B, SLOANE J, LAWLER SD, KAY HEM, LAWSON D, MCELWAIN TJ, ALEXANDER P: Cyclosporin A to prevent graft-versus-host disease in man after allogeneic bone-marrow transplantation. *Lancet* 1980; 1: 327–329

17. CALNE RY, ROLLES K, WHITE DJ, THIRU S, EVANS DB, HENDERSON R, HAMILTON DL, BOONE N, MCMASTER P, GIBBY O, WILLIAMS R: Cyclosporin-A in clinical organ grafting. *Transplant Proc* 1981; 13: 349–358

18. STARZL TE, WEIL R III, IWATSUKI S, KLINTMALM G, SCHRÖTER GPJ, KOEP LJ, IWAKI Y, TERASAKI PI, PORTER KA: The use of cyclosporin A and prednisone in cadaver kidney transplantation. *Surg Gynecol Obstet* 1980; 151: 17–26

19. SWENY P, FARRINGTON K, YOUNIS F, VARGHESE Z, BAILLOD RA, FERNANDO ON, MOORHEAD JF: Sixteen months experience with cyclosporin-A in human kidney transplantation. *Transplant Proc* 1981; 13: 365–367

20. STILLER CR, KEOWN PA, SINCLAIR NR, ULAN RA: Immune responses and pharmacokinetics in the human renal allograft recipient treated with cyclosporin A. In CALNE RY, WHITE DJ (eds): *International Symposium on Cyclosporin A, September 1981, Cambridge, England*, Elsevier, New York (in press)

21. STARZL TE, KLINTMALM GBG, PORTER KA, IWATSUKI S, SCHRÖTER GPJ: Liver transplantation with use of cyclosporin A and prednisone. *N Engl J Med* 1981; 305: 266–269

22. GLUCKMAN E, ARCESE W, DEVERGIE A, BOIRON M: Cyclosporin-A prophylactic treatment of graft-versus-host disease in human allogeneic bone marrow transplantation: preliminary results. Ibid: 368–370

23. MCMASTER P, GIBBY OM, CALNE RY, LOKE M, LUZIO SD, ROLLES K, WHITE DJ, EVANS DB: Human pancreatic transplantation — preliminary studies of carbohydrate control. *Transplant Proc* 1981; 13: 371–373

24. ROUTHIER G, EPSTEIN O, JANOSSY G, THOMAS HC, SHERLOCK S: Effects of cyclosporin A on suppressor and inducer T lymphocytes in primary biliary cirrhosis. *Lancet* 1980; 2: 1223–1226

25. MUELLER W, HERRMANN B: Cyclosporin A for psoriasis (C). *N Engl J Med* 1979; 301: 555

26. ISENBERG DA, SNAITH ML, AL-KHADER AA, COHEN SL, FISHER C, MORROW WJW, MOWBRAY J: Cyclosporin relieves arthralgia, causes angioedema. *N Engl J Med* 1980; 303: 754

27. KEOWN PA, STILLER CR, ULAN RA: Use of cyclosporin-A despite renal dysfunction (C). *N Engl J Med* 1981; 305: 227–228

28. HAMILTON DV, CALNE RY, EVANS DB, HENDERSON RG, THIRU S, WHITE DJG: The effect of long-term cyclosporin A on renal function (C). *Lancet* 1981; 1: 1218–1219

29. MIHATSCH MJ, OLIVIERI W, MARBET U, THIEL G, HARDER F, ZOLLINGER HU: Giant mitochondria in renal tubular cells and cyclosporin A (C). Ibid: 1162–1163

30. SHULMAN H, STRIKER G, DEEG HJ, KENNEDY M, STORB R, THOMAS ED: Nephrotoxicity of cyclosporin A after allogeneic marrow transplantation. *N Engl J Med* 1981; 305: 1392–1395

31. THIRU S, CALNE RY, NAGINGTON J: Lymphoma in renal allograft patients treated with cyclosporin-A as one of the immunosuppressive agents. *Transplant Proc* 1981; 13: 359–364

32. CRAWFORD DH, SWENY P, EDWARDS JMB, JANOSSY G, HOFFBRAND AV: Long-term T-cell-mediated immunity to Epstein–Barr virus in renal-allograft recipients receiving cyclosporin A. *Lancet* 1981; 1: 10–12

## In the next CMAJ

### Safety restraints for children in cars

Why don't more parents use safety restraints for their children? Dr. Verreault and colleagues evaluate the reasons and recommend that physicians, particularly pediatricians, put more effort, energy and imagination into their preventive counselling.

### Involuntary admission to hospital

In 1978 the Ontario Mental Health Act was revised to contain more specific and objective criteria on involuntary admission to hospital and treatment. Although the new requirements have elicited criticism from psychiatrists and other physicians, Drs. Menuck and Littmann describe two cases that indicate that the changes have not obstructed good clinical care and treatment.

### Why I won't practise in Canada

In an interview with Dr. Lazarus Loeb, David Woods, CMA director of publications, found out why the former OMA president went to Texas and why, after briefly considering a return to practise in Ontario, he concluded that Texas is not only bigger but also better.