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Pharmacological immunosuppression in clinical organ grafting. Observations on four agents: cyclosporin A, Asta 5122 (cytimun), lambda carrageenan and promethazine hydrochloride

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SUMMARY

In this article I have attempted to summarize experiments on four agents investigated for immunosuppressive activity in experimental and clinical organ grafting. The difficulty of finding a suitable laboratory model relevant to man has been demonstrated in this experience. A cyclophosphamide-derivative, Asta-5122 (cytimun), has only a marginally superior immunosuppressive activity in a dog with a renal allograft compared with cyclophosphamide and is much inferior to azathioprine. This agent, however, appears to be valuable in clinical practice in patients with liver grafts. A combination of lambda carrageenan, promethazine hydrochloride and imuran has profound immunosuppressive activity in the same canine model, but proved to be both ineffective and potentially toxic in a limited trial in man. The fungal cyclic peptide, cyclosporin A, has been shown to be an extremely powerful immunosuppressive agent and remarkably non-toxic in dogs with renal allografts and pigs with orthotopic heart grafts. This agent is currently being investigated as an immunosuppressant in patients with organ grafts.

INTRODUCTION

Despite extensive clinical experience in the past 15 years using azathioprine and steroids, rejection continues to be the chief cause of failure of grafted organs and approximately 50% of cadaver renal and cardiac grafts cease to function after 2 years (Thirteenth Report of the Human Renal Transplant Registry, 1977). When effective pharmacological immunosuppression was introduced into clinical practice, it was assumed by many investigators that more potent and less toxic agents would soon become available and a large number of compounds were screened. It was found that agents effective in rodents were often toxic or relatively inactive in outbred animals with organ grafts. For example, cyclophosphamide, which is one of the most effective immunosuppressive agents in rodents, is highly toxic to the dog without preventing renal allograft rejection (Zukoski, Callaway & Rhea, 1963).

In man, cyclophosphamide proved to be less effective than azathioprine and more toxic to the bone marrow, although it has a place as an alternative to azathioprine in patients who appear to be sensitive to this drug (Starzl, Weil & Putnam, 1977). The surge of interest in donor-specific immunosuppression led to a waning of enthusiasm for screening pharmacological agents, especially in view of the difficulty in obtaining a model appropriate to man. Enormous effort was expended studying tolerance, enhancement and other forms of donor-specific immunosuppression, all of which can be effective in rodents using specially selected inbred strains. Application of these principles to outbred animals, including man, have been disappointing. Nevertheless, it would seem likely that patients tolerating allografts after a period of time do develop donor-specific graft acceptance, which often allows reduction in dosage of pharmacological agents so that the patients are not bereft of defences against infection.

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Disappointment in progress towards achieving predictable donor-specific immunosuppression has led us to continue studying pharmacological immunosuppression, especially with agents that might be expected to have unusual actions. In this article I will summarize observations on four such agents investigated in outbred mongrel dogs receiving kidney allografts from unrelated animals and, in the case of cyclosporin A, a limited number of experiments in pigs receiving orthotopic allografts from MHC mismatched tissue-typed donors.

The four agents discussed exhibited varying immunosuppressive potencies. The question of clinical application raises difficulties because of the unknown effects in man of treatments with new drugs. The risks must be balanced against the predicted advantages of the new agents compared with current regimens, which, although leaving much to be desired can produce excellent therapy, The first time a new agent is used in man is always worrying for the clinician and he may be tempted to give the drug in doses that are too low for a therapeutic effect. In view of the large number of variables encountered in clinical practice, full appraisal of a new compound may take several years, especially if the patients are also treated with standard immunosuppressive drugs.

METHODS AND RESULTS

Cyclosporin A

This is a peptide metabolite of the fungus *Trichoderma polysporum* studied in a screening programme by Ruëgger *et al.* (1976), of Sandoz and found to have immunosuppressive activity. The compound is a cyclic peptide consisting of eleven amino acids with a molecular weight of 1202·6. It is insoluble in water but soluble in oil and alcohol (Petcher, Weber & Ruëgger, 1976). Biological properties were studied by Borel *et al.* (1976), who found that amongst its other immunosuppressive actions it prolonged skin graft survival from DBA2 donors to BALB/c recipients to 24 days, with a control of 8 days. Animals treated with ALS had skin graft survival of 21 days and with azathioprine 14 days.

On the basis of these reports, Kostakis, White & Calne (1977) investigated the effect of cyclosporin A dissolved in olive oil on heterotopic cardiac allografts in rats and found it to be a very effective immunosuppressant in a model in which WAG(AgB 2) animals were donors and Lewis (AgB 1) were recipients. The mean survival time of hearts in treated animals was 42 days compared with 9 days in controls and animals given olive oil alone.

Calne & White (1977) studied cyclosporin A in mongrel dogs with renal allografts and in pigs with orthotopic heart grafts (Calne *et al.*, 1978a, b). Both survival and renal allograft function were better in the animals treated with cyclosporin A at 50 mg/kg per day than in a control series of animals receiving azathioprine 5 mg/kg per day. Dogs treated with cyclosporin A had a median survival time of 31 days, compared with 10 days for untreated animals and 26 days for twenty-five azathioprine-treated dogs (Table 1). Rejection was the cause of death in 11% of dogs receiving cyclosporin A and 40% of those

TABLE 1. Survival of dogs with renal allografts treated with imuran and cyclosporin A

Imuran		Cyclosporin A	
5 mg/kg		50 mg/kg	
$N = 25$		$N = 17$	
Median 26 days		Median 31 days	
Mean 32 ± 6 days		Mean $> 42 \pm 9$ days	
Cause of death:		Cause of death:	
Infection	12 (48%)	Infection	6 (35%)
Rejection	10 (40%)	Rejection	2 (11%)
Other	3 (12%)	Intussusception	3 (18%)
		Other	3 (18%)
		Alive	3 (18%)

treated with azathioprine. Deaths from infection in the cyclosporin A-treated group were 35%, compared with 48% in the azathioprine group. Four (23%) of the cyclosporin A group were alive between days 50 and 118. In the azathioprine group, two of the twenty-five dogs (8%) survived more than 50 days, whilst eight of the twenty-two animals (36%) treated with cyclosporin A survived more than 50 days. In mismatched orthotopic pig heart grafts, azathioprine at a dose of 5 mg/kg per day had no effect in prolonging survival; both untreated and azathioprine treated pigs died with a median survival time of 6 days. In contrast, five pigs given three doses of cyclosporin A had a median survival time of 22 days. A further six pigs were given 25 mg/kg cyclosporin A daily. Two rejected their hearts at 22 and 43 days after heart grafting. Four are still alive with a median survival in excess of 80 days. Green & Allison (1978) have reported marked prolongation of renal allograft survival in rabbits. Cyclosporin A is more effective in suppressing rejection than any other drug or drug combination we have used in these experimental models. It is remarkably non-toxic, having little effect on the bone marrow but at high doses it does cause weight loss in adult animals and failure to gain normal weight in growing animals. We feel that on the basis of these results cyclosporin A warrants investigation as a clinical immunosuppressant.

Asta 036·5122 (cytimun)

This agent is an analogue of cyclophosphamide (Brock & Kuhlman, 1974). Comparative studies by Botzenhardt & Lemmel (1975; 1976) have shown that this compound has a better therapeutic index as an immunosuppressive drug in mice challenged with sheep red blood cells than cyclophosphamide, azathioprine and 6-mercaptopurine. In non-toxic doses this agent is able to inhibit primary and secondary immune responses. A tolerant-like state was produced after the drug treatment had ceased. We performed experiments in which the drug was given by mouth at a dose varying between 2 and 5 mg/kg per day to dogs with renal allografts. They died between 6 and 8 days, four from infection and one from intussusception (Table 2). All had severely depressed bone marrows, but the renal allografts were functioning. These results are certainly not impressive; they are marginally better than those obtained with cyclophosphamide alone, which caused death from marrow depression without preventing rejection (Zukoski *et al.*, 1963). The dog appears to be more sensitive to alkylating agents than rodents and man.

Cyclophosphamide has been used in patients with liver and kidney grafts with cholestatic jaundice and poor liver function. A number of different protocols were investigated in dogs with renal allografts in which cytimun was combined with azathioprine, the two drugs being given together on alternate days. The results were inferior to those obtained with azathioprine alone. Despite these disappointing observations in the dog, it was felt that cytimun might be a better alternative to azathioprine than cyclophosphamide in patients with liver allografts who were responding poorly to azathioprine.

Case studies. Case 1. A 62-year-old lady with a malignant hepatoma received an orthotopic liver allograft on 21 February 1977. There was no evidence at the time of extra-hepatic spread of the tumour. She was given 100 mg of cyclophosphamide daily for the first 3 days and this was then changed to azathioprine, starting with 100 mg/day and then rising after 5 days to 150 mg. Hydrocortisone (500 mg) was given intravenously on each of the first 2 days and then 250 mg on the third day and subsequently, prednisolone at 75 mg/day for 5 days, dropping to 50 mg/day for 7 days, when it was reduced to 40

TABLE 2. Survival of dogs with renal allografts treated with cytimun

Dose in mg/kg/day	Serum creatinine in mmol/l	Survival in days	Cause of death	White blood count
5	146 on day 8	8	Bronchopneumonia	< 500
3	108 on day 7	7	Intussusception	< 500
3	556 on day 5	6	Bronchopneumonia	1080
2	189 on day 6	7	Bronchopneumonia and intussusception	< 500
2	213 on day 6	7	Bronchopneumonia and bladder haematoma	< 500

mg/day. The patient was discharged from hospital with good liver function on 12 March 1977. She was readmitted on 1 April 1977 with rapidly progressing jaundice. A diagnosis of rejection was made and the prednisolone dosage was increased to 200 mg/day, reducing by 25 mg, on alternate days. The azathioprine was reduced to 125 mg/day on 15 April 1977, but the jaundice increased and the patient developed weakness of the legs and backache, thought to be due to the high steroid dosage. Liver biopsy showed severe cholestatic jaundice with destruction of small bile ducts within the liver and periductal round cell infiltration. On 24 April 1977, 4 months after the transplant, azathioprine was stopped and cytimun was commenced at an average dose of 125 mg. Prednisolone was continued unchanged at 50 mg/day. There was a rapid fall in serum bilirubin levels from 680 μm/l on the day the cytimun was started to 350 μm/l, 3 weeks later on 10 May 1977. The alkaline phosphatase, however, rose from 200 u/l to 700 u/l and remained at about this level. The cytimun dose was maintained at 150 mg/day. Liver function and biopsy appearances remained stable and the patient's general condition improved and she was discharged from hospital. On 27 September 1977 she was readmitted and a further liver biopsy showed little change. A chest X-ray showed secondary growth in the lungs. She was discharged home where she died on 8 October 1977. An autopsy was not performed.

Case 2. A 51-year-old man in the terminal stage of primary biliary cirrhosis received an orthotopic liver transplant on 19 November 1976. He was given cyclophosphamide (100 mg) and hydrocortisone (500 mg) for the first 3 days when the cyclophosphamide was changed to azathioprine, 125 mg, and prednisolone, 75 mg, daily. He was discharged from hospital on 5 December 1976 with a serum bilirubin level that had fallen from a maximum of 240 μm/l to 100 μm/l. The alkaline phosphatase had slowly risen from a minimum of 500 u/l to 1200 u/l. Eight months later he was well, with a serum bilirubin of 12 μm/l and an alkaline phosphatase of 63 u/l. His liver function then started to deteriorate, his bilirubin rose to 252 μm/l and the alkaline phosphatase to 178 u/l. The prednisolone dose was increased to 200 mg daily and the azathioprine was maintained at 150 mg/day. The bilirubin level fell and then rose to a steady state of around 200 μm/l and the alkaline phosphatase rose to 450 u/l. The patient developed severe bone pains with osteoporosis leading to rib and vertebral spontaneous fractures due to high steroid dosage. On 5 October 1977 the azathioprine was stopped and cytimun commenced at 150 mg/day. There was a steady fall in serum bilirubin, which had reached 80 μm/l 3 weeks after starting the cytimun, despite the fact that the prednisolone level had been dropped from 200 to 45 mg/day. The alkaline phosphatase rose to 600 u/l. The serum bilirubin level continued to fall, and the prednisolone dose was further reduced to 12·5 mg and the alkaline phosphatase fell to 250 u/l. His crippling bone pain steadily improved and he was discharged from hospital two months after starting cytimun. He is now well 1¼ years after grafting.

Despite the disappointing immunosuppressive effects of cytimun in dogs with renal allografts, the agent appears to be better than cyclophosphamide. In two patients with liver grafts treated with the drug, immediate subjective and objective improvement followed substitution of cytimun for azathioprine. In both cases the prednisolone dose could be reduced and this was particularly beneficial to the second patient, who was most severely incapacitated by steroid-induced bone disease. In this patient the liver function improved whilst the steroids were reduced. In the first case the effect of the cytimun was less obvious, but the relentless, progressive rejection appeared to be halted by this drug.

Lambda carrageenan and promethazine hydrochloride

More than 20% of cells infiltrating human and renal allografts are macrophages (Nabarra, Descamps & Hamburger, 1975). Lotzova & Cudkowicz (1974) found that the resistance of irradiated mice to parental strain and allogeneic bone marrow grafts could be reduced by the injection of colloidal silica a few days before or after transplantation of the bone marrow cells. Vriesendorp *et al.* (1976) performed similar experiments in dogs, adding intravenous colloidal silica to the standard immunosuppressive regime. This permitted acceptance of marrow grafts from unrelated dogs. Previously, there had been no successful takes of marrow between unrelated animals. Our initial experience using silica in dogs resulted in a high incidence of pulmonary emboli (unpublished observations). We therefore decided to investigate the sulphated polysaccharide, carrageenan, which is known to be toxic to macrophages and can prolong

TABLE 3. Histological assessment of rejection animals dying with serum creatinine levels above 5·1 mg%

Group	Number	Survival (days)	Microscopical rejection grades 0–5 Mononuclear cell infiltration	Arterial lesions	Parenchymal destruction	Overall grading
Animals dying with serum creatinine levels above 5·1 mg%						
1	0					
2	1	20	4	3	2	4
3	3	12	2	4	4	4
		12	3	0	3	2
		15	3	3	3	4
4	4	9	3	2	3	3
		19	4	1	4	4
		30	3	0	3	3
		48	5	3	4	4
Median survival and average grading values of dogs dying with serum creatinine levels below 5·1 mg%						
1	10	22	1·9	0·2	1·7	1·7
2	9	27	1·9	0	1·1	1·7
3	7	24	0·9	0	0·9	1·3
4	6	27	1·3	0	0·7	1·0

survival of skin allografts in mice (Rios & Simmons, 1970). Rumjanek & Brent (1978) have studied immunosuppressive activity of carrageenan and found that although it is a potent suppressor of antibody formation, it is a poor inhibitor of cell-mediated responses. Promethazine hydrochloride has been shown to prolong the survival of cardiac allografts in rats and impair antibody formation in rats and delayed hypertensitivity in guinea-pigs (Jamieson, 1975; Gudson *et al.*, 1969). Attempts have been made to determine the individual and combined roles of lambda carrageenan, promethazine hydrochloride and azathioprine in dogs with renal allografts. The immunosuppressive activity of carrageenan and promethazine hydrochloride alone was insignificant compared with that of azathioprine. When the three were combined, there was marked inhibition of rejection of canine renal allografts which was not observed when either carrageenan or promethazine hydrochloride were combined with azathioprine without a third drug (Calne, Wall & Wilkins, 1974).

A serious complication of the relatively crude 'Gelcarin' carrageenan was acronecrosis, believed to be due to gelation. We therefore investigated purified lambda carrageenan which cannot gelate. The results of four treatment groups of ten animals each are summarized in Tables 3 and 4.

Group (1) were treated on the day of operation with azathioprine, 5·0 mg/kg (Imuran, Burroughs Wellcome) and promethazine hydrochloride, 2·5 mg/kg (Phenergan, May & Baker). For 2 days these drugs were given intravenously and then subsequently by mouth. The first dose of promethazine hydrochloride was given just before the carrageenan, whilst the first dose of azathioprine was given at the end of operation. Purified lambda carrageenan (Batch No. REX 7321, Marine Colloids) was infused intravenously, 5·0 mg/kg in physiological saline (400 mg dissolved in 1·0 litre of physiological saline) 20–30 min prior to the operation. No further carrageenan was administered. Group (2) were treated with azathioprine and promethazine hydrochloride as in Group (1) and were given Gelcarin carrageenan, 5·0 mg/kg (200 mg dissolved in 1·0 litre of physiological saline) as an infusion during the operation. Group (3) were treated with azathioprine and promethazine hydrochloride in the same dose schedule as Group (1), but these dogs were not given carrageenan. Group (4) were treated with azathioprine in the same dose as Group (1).

There were no significant differences in the median survival times (MST) between the four treatment groups. In the carrageenan-treated animals, groups (1) and (2), the chief cause of death was bilateral

TABLE 4. Data on the four treatment groups of dogs with renal allografts

Immunosuppressive treatment (ten dogs in each group)	Mean creatinine in mg% (±s.e.m.) at: Tenth day	Final day	Median survival time (days)	Number of deaths from uraemia	Number of deaths from pneumonia	Acronecrosis
Group 1 Lambda carrageenan+ Imuran+ Phenergan	2·3±0·4	2·5±0·5	22	0	9	0
Group 2 Gelcarin+ Imuran+ Phenergan	1·8±0·4	2·4±0·7	23	1	6	3
Group 3 Imuran+ Phenergan	4·1±1·2	5·8±1·7	18	3	6	0
Group 4 Imuran	3·3±0·8	6·0±1·7	27	4	5	0

pneumonia which had similar gross and microscopical appearances to the pneumonia seen in the animals treated with azathioprine alone. Three dogs receiving Gelcarin carrageenan developed necrosis of one or more paws. None of the animals that received purified lambda carrageenan developed this complication. There was no significant difference between the Gelcarin and lambda carrageenan groups, (1) and (2), when the deaths from uraemia or the function of the grafts, as measured by the serum creatinine levels at day 10 and at death, were compared. Similarly, there was no significant difference in the same observations compared between the azathioprine and promethazine and azathioprine alone, groups (3) and (4). The twenty dogs that received carrageenan, groups (1) and (2), were therefore compared with the twenty animals that received imuran and promethazine hydrochloride and imuran alone, groups (3) and (4), which acted as controls. A significant difference was found in the serum creatinine levels on the tenth day ($P<0·05$), and on the last day ($P<0·01$). The incidence of the deaths from uraemia were also significantly different ($P<0·05$). Thus, although the survival of the animals was not prolonged, there was better graft function in the dogs that received Gelcarin or lambda carrageenan as part of their drug treatment.

Table 3 shows the correlation between uraemia as a cause of death and the grade of rejection. The incidence of important arterial lesions was closely correlated with uraemia. Of the animals dying without uraemia in all groups, there were no striking differences at death to distinguish one group from the others. The histological features of rejection in the animals dying with uraemia was similar in all groups.

No unusual granulomatous lesions were seen in the organs and tissues of the carrageenan-treated animals, but in the animals with acronecrosis there were thrombi in capillaries and veins related to the necrotic tissue. Many thrombi were being organized and their appearance suggested that they were an important factor in the development of the necrosis rather than a consequence of tissue death.

The mode of action of lambda carrageenan, azathioprine and promethazine hydrochloride in suppressing the rejection of renal allografts in dogs is not established. Since carrageenan was given in one dose prior to surgery, it is likely that it acts on the initial recognition and/or antigen processing phase of the immune reaction. The antihistamine effect of promethazine hydrochloride could impair allergic damage. In high doses carrageenan has a heparin-like effect, but in our experiments clotting time was not prolonged beyond a few minutes. On the basis of the experiments referred to in dogs, a pilot study was undertaken using purified lambda carrageenan and promethazine hydrochloride in addition to azathioprine and steroids in clinical kidney grafting.

Case studies. Case 1. A 50-year-old man suffering from end-stage diabetic glomerular sclerosis had rejected after four months a one haplotype matched kidney transplanted from his sister. He was returned

to dialysis and developed Australia antigenaemia. He was in a poor general condition with some 30 litres of excess fluid in the extracellular spaces and was anxious to try any new procedure that might give him a better chance with the second kidney. The experimental nature of the therapy was explained to him. Prior to anaesthesia he was given 50 mg of phenergan intravenously and 400 mg of purified lambda carrageenan in 500 ml saline. There was no change in the patient's blood pressure or ECG, although the heart rate increased to 125 beats per min and he experienced slight substernal discomfort. Anaesthesia was induced and the infusion was continued. The patient was transplanted with a four antigen mismatched cadaver kidney. Following the operation, there was no evidence of adverse effects of carrageenan; he was given 50 mg of phenergan a day and standard steroid dosage. Renal function was initially poor and diuresis began 8 days after the operation. His general condition deteriorated and he developed septicaemia and pneumonia, dying 23 days after transplantation with a kidney functioning well and a serum creatinine of 3·0 mg%.

Subsequent cases were given the same regimen of treatment with carrageenan, promethazine and azathioprine.

Case 2. A 48-year-old woman with end-stage pyelonephritis received a cadaver graft which never functioned and was removed 3 weeks later and found to be infarcted with renal artery and venous thrombosis. A second transplant was performed a year later, this time treatment was with azathioprine and steroids only. She is well at present with good renal function 11 months after grafting.

Case 3. A 48-year-old woman with hypertensive renal failure was prepared for renal transplantation by preliminary bilateral nephrectomy at which time gall stones were found and cholecystectomy was performed. Three weeks after being discharged from hospital she was admitted *in extremis* with a faecal peritonitis from a spontaneous perforation of the pelvic colon. A colostomy and sigmoid colectomy were performed from which she recovered after a stormy post-operative phase. The colostomy was closed and she was considered to be an extremely poor risk for steroid therapy. A cadaver kidney became available and she was transplanted with immunosuppression consisting of carrageenan, promethazine hydrochloride and azathioprine as in the first case, but with no steroid. Renal function became satisfactory, but in view of a possible rejection crisis 10 days later, steroids were started. This patient is well and has good function in her graft 1½ years after transplantation.

Case 4. A 52-year-old man with glomerular nephritis received a cadaver allograft and was treated with carrageenan, promethazine hydrochloride, azathioprine and steroids. He developed moderate hypotension during the infusion of carrageenan and there was severe operative haemorrhage which recurred after the operation. The wound was re-explored to stop the haemorrhage. Haematological tests showed a heparin-like effect which was presumably an adverse reaction to carrageenan. The patient recovered and has currently good function in the kidney 1¼ years after transplantation.

Case 5. A 44-year-old man with glomerular nephritis received a cadaver allograft and was treated in a similar way to Case 4. There was moderate hypotension during infusion of carrageenan. The transplant functioned for 3 months and then the patient developed severe herpes simplex and evidence of septicaemia. Renal function had deteriorated and the kidney was removed and showed chronic rejection and local sepsis. The patient died a month later from heart failure.

Case 6. A 44-year-old woman with glomerular nephritis and pyelonephritis received an allograft and was treated as Case 4. There was no hypotension or other complications during the infusion of carrageenan. The transplant showed initial poor function. A biopsy at 6 weeks showed mild rejection. Function did not improve and the kidney was removed and found to be infarcted. Vascular occlusion must have occurred subsequent to the biopsy at 6 weeks. The patient is alive on dialysis.

Case 7. A 38-year-old man with glomerular nephritis received a cadaver transplant with conventional immunosuppression. The kidney was rejected and then removed 2 months later. Six months later he received a second cadaver transplant and was treated with carrageenan and promethazine as Case 4. There was a hypotensive episode during the infusion of the carrageenan. The kidney never functioned and biopsy at 4 days showed severe rejection with vascular change. The patient died 7 months later from pneumonitis with pneumocystitis infection.

Case 8. A 23-year-old woman with end-stage pyelonephritis received a cadaver transplant and was

treated as Case 4. There was moderate hypotension during the operation. The kidney functioned but the patient developed severe wound infection, which led to septicaemia and renal artery and vein thrombosis. She died from the effects of sepsis 3 weeks after the transplant.

It is clear that the carrageenan and promethazine hydrochloride did not add to the therapeutic efficacy of azathioprine and steroids in these patients, compared with standard immunosuppressive therapy. In addition, some patients developed hypotension whilst the carrageenan was being infused and one patient developed severe coagulopathy. Promethazine hydrochloride caused drowsiness at 50 mg dosage.

DISCUSSION

The data on the four agents demonstrate some of the difficulties involved in developing new immunosuppressive drugs in clinical practice. The moderately promising experimental results with a combination of lambda carrageenan and promethazine hydrochloride were not borne out in a limited clinical trial. Carrageenan has dangerous side effects and the promethazine hydrochloride is also not well tolerated in large doses. The cyclophosphamide derivative, cytimun, had disappointing experimental effects; nevertheless on the basis of pilot studies in two patients it appeared to be a useful immunosuppressive agent in two liver transplant patients who responded poorly to azathioprine. The fungal peptide cyclosporin A has been carefully evaluated in animal experiments and appears to be the most promising immunosuppressive drug yet investigated in animals with organ grafts and we propose to study this drug clinically. The good results of kidney grafting are well-known, but the disasters resulting from rejection are still common and better immunosuppressive therapy would prevent much suffering.

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