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Pharmacology of Cyclosporine (Sandimmune)
I. Introduction

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A. Importance of Cyclosporine

In recent years the pace of publications on cyclosporine (CS)† has increased to approximately 2000 papers per annum (fig. 1). What is it that generates such an unprecedented interest in a novel compound? The cause is essentially 2-fold. On the one hand, CS is the first selective immunosuppressive drug; on the other, it is widely used as an experimental probe.

Advances in basic immunology increasingly reveal the complexities of the immune system. The former use of unspecific cytostatic or lymphocytotoxic agents to suppress the immune response is today being replaced by more specific, i.e., immunopharmacological, approaches. However, the pharmacological or biological modulation of a single component of the immunoregulatory network might still perturb the entire system, thereby diminishing the specificity of the intervention. The powerful immunosuppressive activity of CS, which is apparently restricted at the cellular level of certain T lymphocytes, is recognised as the breakthrough in immunopharmacology. (For recent reviews see refs. 5, 19, 23, 29, 49, 52.)

The pharmacological spectrum of CS has many facets (fig. 2). Because of its potent inhibition of the antibody- and cell-mediated immune response, CS is now being used as the mainstay in clinical immunosuppression. After a difficult learning process in which the efficacy and the side effects of the drug were explored, CS has proved to be of permanent clinical value and has, in consequence, revitalised the field of organ transplantation (6, 41). CS has significantly improved the survival of kidney, liver, and heart allografts and is opening up the way for the transplantation of other organs such as heart and lung en block, lung, skin, nerves, blood vessels, bone, small bowel, etc. Because of its steroid-sparing effect (36, 38), it has greatly extended the eligibility of patients for transplantation; e.g., children and the elderly, and diabetic and black patients (17). Presensitised high-risk patients have also become suitable graft recipients. (1; for review see relevant chapters in ref. 2). A combination of CS with total lymphoid irradiation might even open the door to xenograft transplantation. Since CS therapy leads to a better quality of life (14, 33, 42) and is cost-effective (40, 43), it has created tremendous ethical problems related to organ shortage (e.g., selling organs, and using fetal tissues and tissues from anencephalic newborns).

In contrast to classical immunosuppressants, CS exerts a specific action on lymphocytes and does not interfere with the functions of phagocytes or haemopoietic stem cells. It is neither lymphocytotoxic, as its action is reversible, nor mutagenic. Nephrotoxicity, its major side effect, can largely be minimised by drug combinations, especially in the early stages, or by dose reduction during the maintenance phase (27, 31). The prospects of refining protocols further and thus improving the results and avoiding the other more trivial side effects (for review see refs. 24, 26 and 28) remain reasonably optimistic and widen the scope of immunosuppression.

CS is a powerful inhibitor of chronic or immune-mediated inflammatory reactions, but has no effect in models of acute inflammation. Its importance for exploring the pathogenesis and treating some acute and chronic inflammatory diseases generally grouped as suspected autoimmune diseases is clearly emerging in the clinic, although its value has not yet been fully assessed (for review see refs. 45). The use of CS in treating several such diseases has revealed its potential to counteract the imbalance of the immune system by improving the condition of both experimental animals (10) and patients (for review see ref. 18).

Besides being an immunosuppressive drug, CS is also widely used as an experimental probe in basic research. Thus, for immunologists, it has become an important pharmacological tool for defining in vitro the respective roles of cell interactions and mediators in lymphocyte activation, analysing the cell regulatory mechanism of the genes, and studying the different steps involved in an immune response in general. CS makes it possible to

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† Abbreviation used is: CS, cyclosporine.

evaluate the contribution of various T cells not only in normal but also in pathological conditions. Thus, the inhibition of smooth muscle proliferation in the vascular response to injury observed in CS treatment of rats demonstrated that this proliferation is mediated via the immune system (22). Another example is the discovery, resulting from the use of CS in experimental models (30, 46) and in clinical trials, of the underlying autoimmune mechanism in insulin-dependent diabetes mellitus type I and in psoriasis (11, 16, 51). It should also be mentioned in this context that the antiparasitic effects of CS were first observed when it was used as a tool to deplete mouse T cells to evaluate their significance in schistosomiasis (12) and malaria (47). It was demonstrated that this novel activity against several parasitic infections is independent of the immunosuppressive effect, since weak or non-immunosuppressive analogues exert similar potency to CS. In addition, CS is now the reference drug in the search for new immunosuppressants. Chemists have studied its structure-activity relationship and used it to try to create new chemical entities.

Although CS was first tested as an antibiotic, its fungicidal activity is of no clinical value since, with the exception of coccidioidomycosis (20, 25), CS remains ineffective against human pathogens. A recent addition to its pharmacological spectrum is the discovery that CS, like weak or non-immunosuppressive derivatives, can reverse multidrug resistance experimentally both in vitro and in vivo (for review see ref. 50).

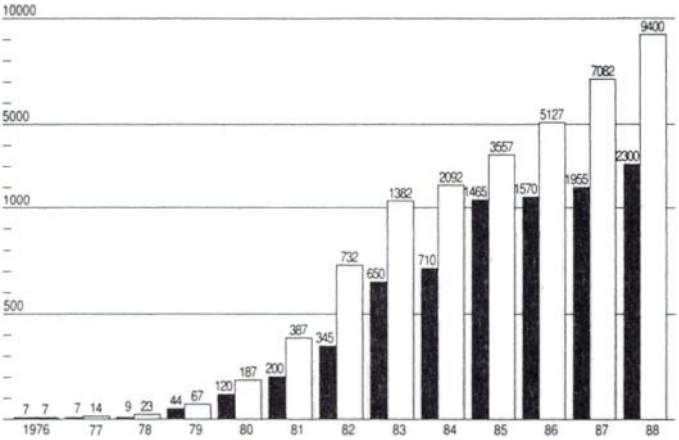

FIG. 1. The growing number of publications on cyclosporine over the years is represented on a logarithmic scale. The first paper appeared in late 1976. Black columns, number of publications for each year; white columns, cumulative numbers over the years.

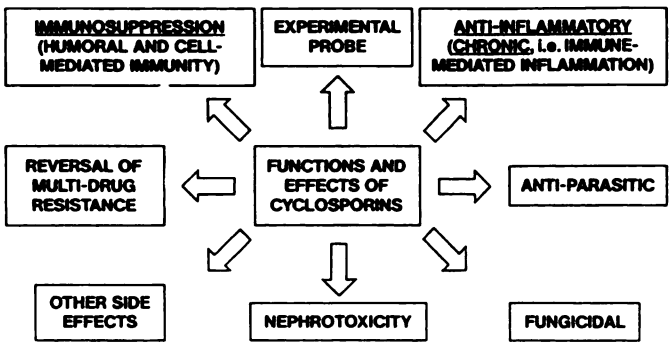

FIG. 2. Pharmacological spectrum of CS.

B. Aim of the Review

CS is one of a family of fungal metabolites that has proved to be a potent immunosuppressant (53). We shall restrict ourselves to the pharmacology of CS, formerly called cyclosporin A. Other analogues or derivatives will be mentioned only in exceptional cases, especially in the part on chemistry, where they are needed to demonstrate the structure-activity relationship, and in those instances in which their pharmacological or toxicological spectrum is at variance with that of CS (for reviews see refs. 7, 54, 55).

The purpose of this review is to cover all pharmacological aspects of CS; however, clinical results will be referred to (mainly as review papers) when they confirm or extend these aspects. Experimental and clinical research with CS has progressed so rapidly that it becomes increasingly difficult to select the relevant publications from the flood of literature. Moreover, CS has recently spread into widely different fields, often causing information to be dispersed and incompletely accessible. It is our aim to concentrate on the most relevant work (until 1988) contributing to our basic knowledge of CS. In addition, to help form a personal and balanced opinion from the many contradictory reports, we shall select those we consider to be the most original and discuss fundamental controversial issues by attempting a critical analysis of possible reasons for disagreement. Thus, difficulties in comparing data from apparently similar experiments that differ in crucial methodological concepts will be emphasised, and the dichotomy between several in vitro and in vivo findings will also be addressed. Accordingly, the reference list includes the most pertinent and recent papers, but is far from being exhaustive.

C. Historical Background

The eventful and tortuous history of CS (table 1), starting with the soil sample collected from the Hardanger Vidda in Norway, from which the CS-producing fungus was grown, has been recollected elsewhere (4, 44). The cyclosporines were originally discovered in the early seventies by workers at Sandoz Ltd. in Basel Switzerland who were routinely screening for new agents with antifungal antibiotic activity (15, 37). The crude extracts of two strains of fungi imperfecti, *Cylindrocarpon lucidum* Booth and *Tolypocladium inflatum* Gams, possessed antifungal activity, though this subsequently proved to be of insufficient interest to warrant particular development. However, this activity was coupled with an unusually low toxicity in mice. This was an important factor in the decision to submit the metabolite mixture to a limited pharmacological screening programme. In early 1972, J. F. Borel discovered that the fungal extract was capable of markedly suppressing haemagglutinin forma-

TABLE 1
The development of cyclosporine in brief

1970	B. Thiele: Isolation of two new strains of fungi imperfecti producing antifungal metabolites.
	Z. L. Kis et al.: Isolation of a metabolite mixture and characterization as novel neutral polypeptides.
1971	Haerri/Rüegger: Isolation of the partially purified two-component metabolite mixture (24-556) on a preparative scale for initial biological screening.
1972	Borel: Discovery of immunosuppressive properties of metabolite 24-556 in rodents.
1973	Ruëgger: Purification of CS (27-400).
	Dreyfuss et al.: Culture and production of CS.
1974	Borel et al.: Animal studies of the immunosuppressive activity of CS, in vivo and in vitro.
1975	Petcher et al./Rüegger et al.: Elucidation of the structure of CS (X-ray studies and chemical degradation).
1976	Toxicity studies (rats, monkeys) demonstrate selectivity of CS for lymphocytes and lack of effect on haemopoiesis.
	World-wide confirmation of specific immunosuppressive effect of CS in experimental transplantations and other models.
1978	Calne et al., Powles et al.: First clinical trials (kidney transplantation, graft-versus-host disease).
1980	Wenger: Total synthesis of CS.
1981	Bueding et al./Thommen: Publication of antischistosomal and antimalarial activity of CS.
1983	Sandimmune first registered in Switzerland; same year also in the United States and some other countries.
1985	First controlled clinical trials in autoimmune diseases.

tion against sheep erythrocytes in mice, and H. Stähelin observed that it would not prolong the survival time following inoculation with the murine leukaemia cell line L 1210 in the same animals and did not have any effect on mouse tumour cells P 815 in vitro (4). This was a clear indication that immunosuppression was not linked with general cytostatic activity! Subsequent extensive studies of the pharmacological effects of CS by Borel and coworkers revealed that CS, which was eventually purified in 1973 (15, 37), exerted unique immunosuppressive effects, while sparing the haemopoietic tissues (8, 9). This selective and reversible action on lymphoid cells, together with its novel chemical structure, made CS the prototype of a new generation of immunosuppressants. Indeed, the likelihood that other similar metabolites will be discovered or that related molecules will be synthesised in the future should be borne in mind (3, 21, 32, 34, 39, 48).

After CS's ability to protect organ allografts from rejection had been convincingly demonstrated in many animal models, the immunosuppressive effects were tested in man. In June 1978, the first patients were being investigated by Sir Roy Calne (Cambridge) in mismatched cadaver kidney transplantation (13), and by R. L. Powles (Royal Marsden, Sutton) in bone marrow transplantation (35). Finally, in 1983, CS was registered first in Switzerland under the registered trademark Sandimmune for organ transplantation, then later the same year in the United States. The story concludes with many years of painstaking efforts by dozens of scientists from various specialities being crowned with success.

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