Leading articles

Immunomodulating effects of antimicrobial agents

Antimitotic agents are well known for their depressant effect upon the immune system and are used to advantage in both organ transplantation and in the management of immune mediated disease. In contrast the action of antimicrobial agents on the immune system is largely ignored in clinical practice, although a variety of effects—mostly in experimental systems—on both cell mediated and humoral immunity have been recognized.

The relevance of many of these observations is probably minor since antimicrobial chemotherapy is usually short-lived. However, the treatment of tuberculosis, leprosy, deep seated bone infection, systemic mycoses and acne vulgaris and the chemoprophylaxis of rheumatic fever and recurrent urinary tract infections require protracted therapy. Immune mechanisms play an integral part in the pathogenesis of several of these conditions and are also important for recovery. It is therefore appropriate that there should be an awareness of the potential effects of antimicrobial agents on the immune system. Among the many antimicrobial agents that have been studied, rifampicin, the tetracyclines and the cephalosporins have attracted most attention.

In vitro, rifampicin produces dose-dependent suppression of human lymphocyte blastogenesis by the non-specific mitogen, phytohaemagglutinin (PHA) (Grassi & Pozzi, 1972; Serrou, 1974), as well as by the specific mitogen PPD (Nilsson, 1971; Dajani, Kasik & Thompson, 1973). A similar effect with the B cell mitogen, Cowen 1 Staphylocococcus aureus, is also seen (Banck & Forsgren, 1979). Secretion of migration inhibition factor by lymphocytes is suppressed (Serrou, 1974). Skin allograft survival in rabbits (Serrou et al., 1972) and pancreatic graft survival in dogs (Serrou, 1974) is prolonged.

In patients receiving rifampicin for tuberculosis, skin reactivity to PPD is progressively yet reversibly reduced (Ruben, Winkelstein & Fotiadis, 1974). Furthermore, suppression of skin hypersensitivity to dinitrochlorobenzene (DNCB), BCG, PPD and bovine serum albumin (BSA) in guinea-pigs is also recognized (Dajani et al., 1973; Grassi & Pozzi, 1972; Paunescu, 1970). Despite observations that skin hypersensitivity to tubercle bacilli is suppressed by rifampicin, it appears that immunity to tuberculous infection in previously infected or immunized animals is not impaired (Youmans, Youmans & Cahall, 1976).

The effects of rifampicin on antibody response in man are variable. Seroconversion to smallpox vaccination is suppressed when rifampicin is applied topically, an effect which is over and above the known antiviral properties of this agent (Moschkowitz, Goldblum & Heller, 1971). Oral rifampicin also interferes with antibody response to keyhole limpet haemocyanin (Graber et al., 1973). However, the antibody response to influenza and cholera vaccines appears unaffected (Ruben et al., 1974; Bassi et al., 1973). In guinea-pigs and rabbits the primary antibody response to BSA is suppressed (Paunescu, 1970) as is the response in mice and guinea-pigs to sheep erythrocytes (Paunescu, 1970; Bassi et al., 1973; Dajani et al., 1973).

Phagocytic function of peripheral blood leukocytes is unimpaired by rifampicin (Hoeprich & Martin, 1970) although chemotaxis is quite markedly suppressed (Forsgren & Schmeling, 1977). A suppressive effect on mouse peritoneal macrophages treated with intraperitoneal rifampicin can also be demonstrated (Bassi et al., 1973). Among the tetracyclines, doxycycline and minocycline in particular, and to a lesser degree oxytetracycline and tetracycline, but not lymecycline, suppress PHA and pokeweed mitogen (PWM) induced lymphocyte transformation (Banck & Forsgren, 1979; Thong & Ferrante, 1979). A similar suppression of B lymphocyte responsiveness to Cowan 1 Staph. aureus is seen with doxycycline as is the antibody response by B-lymphocytes, as measured by plaque assay (Banck & Forsgren, 1979).
Tetracycline is readily taken up by leucocytes resulting in high intracellular concentrations (Park & Dow, 1970), which may be relevant to the varied effects of tetracyclines on phagocytic function. This in turn could be important for recovery from infection, since the action of tetracyclines is primarily bacteriostatic. Doxycycline produces dose-dependent suppression of phagocytosis of opsonized yeast in vitro, while leucocytes harvested from volunteers on therapeutic levels of tetracycline HCl also demonstrate impaired phagocytosis of opsonized yeast (Forsgren, Schmeling & Quie, 1974). Chlortetracycline similarly inhibits engulfment in vitro, although tetracycline HCl does not (Munoz & Geister, 1950; Hoeprich & Martin, 1970). Tetracycline HCl, oxytetracycline, lymecycline and doxycycline all suppress the serum bactericidal action on Escherichia coli, an effect that is reversed by the addition of magnesium ions (Forsgren & Gnarpe, 1973).

Both spontaneous and induced migration of polymorphonuclear cells is impaired by doxycycline and to a lesser extent by lymecycline in vitro, (Belshem, Gnarpe & Persson, 1979; Forsgren & Schmeling, 1977). Such impairment has been demonstrated in leucocytes derived from volunteers, as well as from patients with post-operative wound infections receiving doxycycline (Belshem et al., 1979).

Penicillins do not appear to affect in vitro tests of cell mediated immunity (Banck & Forsgren, 1979). However, the same is not so for the cephalosporins despite their structural similarity. Cephalothin, cephradine, cephalaxin, cefamandole, cepharin, cefazolin and cefoxitin produce a dose-dependent reduction in the lymphocyte response to PHA, PWM and concanavalin A. This reduction is greatest for cephradine and cephalaxin which share a similar structure (Chaperon & Sanders, 1978; Banck & Forsgren, 1979). Most of these effects are observed at concentrations that exceed therapeutic levels, except in the case of cephalothin and possibly cefamandole.

Prolongation of skin graft survival by trimethoprim in mice is comparable to that achieved with azathioprine (Gillichick, Morris & Reeves, 1970). Trimethoprim and sulphamethoxazole in the therapeutic ratio of 1:5 also show a dose-dependent depression of PHA induced blastogenesis by human lymphocytes (Gaylarde & Sarkany, 1972) although each agent alone shows very little effect (Banck & Forsgren, 1979). Humoral immunity is also affected, antitoxin titres to tetanus toxoid are reduced in volunteers prescribed a therapeutic dosage of cotrimoxazole (Arvilommi, Vuori & Salmi, 1972).

Several other antimicrobial agents including clindamycin, erythromycin and nitrofurantoin impair blastogenesis at concentrations that exceed those achieved therapeutically although fusidic acid does so at 1 mg/l and even more markedly at 10 mg/l. In addition, protein synthesis, as measured by 14C leucine uptake, and antibody production, as determined by plaque assay, are impaired by nitrofurantoin and fusidic acid, although at levels in excess of those achieved therapeutically (Banck & Forsgren, 1979). Fusidic acid also significantly suppresses leucocyte chemotaxis at therapeutic concentrations (Forsgren & Schmeling, 1977). Antifungal agents produce contrasting effects. 5-fluorocytosine does not inhibit PHA induced blastogenesis (Banck & Forsgren, 1979) although amphotericin B, clotrimazole and miconazole do, (Tarnvik & Ansehn, 1974; Thong & Rowan-Kelly, 1978). Only miconazole does so at therapeutically achievable concentrations. Furthermore, the effect of clotrimazole shows progressive diminution with the presence of increasing concentrations of serum (Thong & Rowan-Kelly, 1978).

Despite its marrow toxicity chloramphenicol has little effect on lymphocyte blastogenesis induced by PHA, PWM or Con A (Banck & Forsgren, 1979) although cell division is inhibited (Pisciotta & DePrey, 1967). However, blastogenesis in response to candida antigen or streptokinase-streptodornase is depressed (DaMert & Sohnie, 1979). Neutrophil chemotaxis is also suppressed (Forsgren & Schmeling, 1977). Other commonly used agents including penicillin, carbemcillin, gentamicin, kanamycin, nalidixic acid and streptomycin appear to have no effect on lymphocyte blastogenesis (Chaperon & Sanders, 1978; Banck & Forsgren, 1979).

Many of these observations are unlikely to have clinical significance since they occur at concentrations that exceed those achieved therapeutically. On the other hand, rifampicin, doxycycline, minocycline, tetracycline, cephradine, cephalaxin, cefamandole, nalidixic acid, cotrimoxazole and fusidic acid produce their effects at therapeutic levels although admittedly these are often short-lived. It would therefore appear that in the
management of most acute infections requiring antimicrobial chemotherapy such laboratory observations need attract little consideration, particularly since such obvious benefit accrues from the use of these agents.

Nonetheless, in situations where long-term chemotherapy is employed, as in the management of mycobacterial infections, immune mechanisms are known to be important in both the pathogenesis and recovery from disease. Such infections are frequently opportunistic and occur in patients already immunocompromised by virtue of underlying malignant disease or as a result of antimicrobial or immuno-suppressive therapy. Under these circumstances the recognition of the immuno-modulating effects of antimicrobial agents may have therapeutic significance and deserves further consideration.

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References
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The potential of phosphonformate for the treatment of herpes simplex labialis

Herpes simplex labialis or cold sores is the most common disease in man caused by HSV type 1. The infection is often recurrent, representing reactivation of latent virus residing in the trigeminal ganglion. It has been estimated that 7% of the population of the USA has more than two episodes of recurrent HSL per year (Overall, 1979). In epidemiological terms this is an important uncontrolled infection, while in terms of the clinical use of antiviral drugs the infection represents an ideal target where compounds can be used topically. It is rather surprising then that more attention has not been directed in the past towards this troublesome disease. This situation may now change dramatically with the advent of a simple molecule sodium phosphonofomate (Helgstrand et al., 1978). This compound is related to the parent phosphonoacetic acid (Shipkowitz et al., 1973) but has the advantage of non-toxicity following application on the skin. In addition phosphonofomate (PFA) has a rather different antiviral spectrum: as well as anti herpes type I and II activity PFA inhibits DNA polymerase of hepatitis B virus (Nordenfelt, Helgstrand & Oberg, 1979). Careful laboratory studies have established that PFA inhibits the DNA polymerase of HSV-1 and HSV-2 viruses, possibly by acting as a non-competitive inhibitor at the pyrophosphate binding site on the enzyme itself. Work in animal model infections, particularly infection of guinea pig skin, has established a marked therapeutic activity of PFA (Alenius, Dinter & Oberg, 1978). In this model infection a depilated area of the skin is punctured lightly with a gun and infected with HSV-1 and 24 h later an erythema is detected. Addition of 2% PFA as a topical cream six times daily thereafter results in a marked therapeutic activity both measured as a cumulative score and on a time to healing parameter. Other compounds such as idoxuridine ribavirin, acyclovir, cytosine arabinoside are less effective in this model system (reviewed by Collier & Oxford, 1980). A relevant observation of these studies is that the vehicle or ointment used to apply the antiviral compound is of considerable importance, and more attention is needed on parameters of drug adsorption and solubility. Preliminary clinical trials reported at the antiviral meetings at the London Hospital in November 1979 and in Atlanta in March 1980 have described a therapeutic effect of PFA in man. The therapeutic efficacy of 3% ointment used six times daily for 4 days was studied in a multicentre double blind, placebo controlled trial in patients with a history of recurrent herpes labialis (Wallin, Lernestedt & Lycke, 1980). Two-hundred episodes of current disease have been studied to date. At the time of the first episode the patient was randomly assigned to the control or active treatment group. At the first episode treatment was begun within 24 h whereas after cross over and with the next episode the patients used self-medication immediately clinical signs were obvious. At the first episode lesion size and stage were measured at the clinic and, in addition, each patient kept a record of pain score and lesion development. PFA significantly shortened the papular and vesicular stages of the disease and significantly more patients in the control group developed new vesicles. Of particular interest for future clinical trials, it was noted that many patients were ‘well able to discriminate between active and placebo treatment in spite of a high comparability of objective measurements’. In short, patients derived a beneficial effect from treatment—a consideration easily overlooked in initial double blind scientifically controlled trials! Obviously these trials will have to be confirmed, but at this stage the data appear rather convincing. A cloud on the horizon concerns the ability of absorbed PFA to bind tightly, but not irreversibly, to the inorganic matrix of bone. To date no adverse toxicological effects of this binding has been noted in animal models. Of course tetracyclines bind rather strongly to certain bone tissues but this has not obstructed unduly the therapeutic use of this group of compounds. Acyclovir, another anti-HSV compound acting also as an inhibitor of HSV DNA polymerase (Schaeffer et al., 1978) is now undergoing extensive clinical trials with herpes encephalitis, genitalis and labialis. Without being too pessimistic one should note that drug resistant herpes virus mutants to both compounds can be obtained with relative ease, including strains resistant to both ACV and PFA and the possible emergence of such viruses is being carefully monitored in clinical trials. Both compounds are relatively cheap and easy to manufacture