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Letters to the Editor

POSSIBLE INCOMPATIBILITY OF DAPSONE WITH CLOFAZIMINE IN THE TREATMENT OF PATIENTS WITH ERYTHEMA NODOSUM LEPROSUM

Sir,

During the last 5 years we have investigated the effects of the anti-mycobacterial drugs dapsone and clofazimine (Lamprene (R) or B663) on cellular and humoral immune functions. We have formed the impression that clofazimine and dapsone may be antagonistic in the treatment of the condition erythema nodosum leprosum (ENL). We wish to emphasize, however, that our investigations relate only to the possible inhibitory effects of dapsone on the anti-inflammatory activity of clofazimine in individuals with ENL.

Starting in 1972, a study was made of a group of BL and LL patients (9 males, 7 females) who were suffering from severe recurrent ENL and had been treated with dapsone and clofazimine for an average of 21 months. In addition to dapsone 5 patients needed 500 mg of clofazimine, 6 needed 400 mg, 3 needed 300 mg and 2 needed 200 mg daily. Despite these rather high doses of clofazimine the ENL was not controlled and 14 patients required additional therapy with corticosteroids. When dapsone was discontinued these patients responded to clofazimine alone. The high doses of clofazimine were gradually reduced to 300 mg weekly and in cases where ENL re-occurred it was controlled by an increase in the clofazimine dosage. Under this regimen corticosteroids were unnecessary.

The results of this trial were never published because the study group was small and uncontrolled. However, in a letter to Ciba Geigy Ltd (7 May 1980) one of us (FMJHI) expressed doubts about the efficacy of the combination of dapsone and clofazimine in controlling patients with ENL. Recent laboratory evidence adds substance to these doubts. Table 1 shows the effects of the dapsone–clofazimine combination on the *in vitro* migration of neutrophils from leprosy patients. In these studies the leucoattractant used was endotoxin-activated autologous serum (EAS) and the solvent for clofazimine was dimethyl sulphoxide for which control systems were included. It can be clearly seen that clofazimine inhibits neutrophil motility and that 10^{-3} M dapsone overcomes the clofazimine effect.

We have previously shown that dapsone can stimulate neutrophil motility by mediating

Table 1. The effects of co-incubation of clofazamine with migration-stimulatory concentrations of dapsone on the migration of neutrophils from leprosy patients to autologous EAS

Test system	Migration responsiveness to EAS
Neutrophils + HBSS (control)	$76 \pm 26^{*}$
Neutrophils + 10^{-4} M lamprene	$36 \pm 14^{\dagger}$
Neutrophils + 10^{-4} M lamprene + 1×10^{-3} M dapsone	$131 \pm 40^{\ddagger}$

*Results as mean neutrophils/HPF with standard error of five separate experiments.
†$P < 0.05$ for inhibition of migration.
‡$P < 0.05$ for stimulation of migration.

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inhibition of the peroxidase – H_2O_2 – halide system *in vitro*.[1] Clofazimine would appear to have the opposite effect to dapsone.

The results shown in Table 1 suggest that dapsone may decrease the anti-inflammatory activity of clofazimine and therefore possibly necessitate the use of high clofazimine dosages to control ENL. This theory pre-supposes a role for the neutrophil in the pathology of ENL, which is probably a type III immunological hypersensitivity reaction (immune complex or Arthus type). The neutrophil has been demonstrated to contribute to the inflammation and tissue damage in these reactions by releasing toxic oxygen radicals (superoxide anion and hydroxyl radical) and proteolytic enzymes.[2] It therefore seems reasonable to suggest that agents such as clofazimine which inhibit neutrophil migration may control the inflammation by decreasing the numbers of neutrophils in regions of inflammation. On the other hand agents such as dapsone which potentiate neutrophil migratory responsiveness may nullify the anti-inflammatory effects of clofazimine.

Finally we wish to stress that these observations relate only to the possible inhibitory effects of dapsone on the anti-inflammatory activity of clofazimine and must not be confused with the beneficial effects of the combination of clofazimine and dapsone in the treatment of cases with drug-resistant *Mycobacterium leprae*.

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