

anti-infective action of vitamin A could be associated with an increase in the susceptibility to malaria infection. Therefore, further investigation is clearly needed before the use of the combined supplementation of iron and vitamin A is recommended for malaria endemic areas.

A second consideration relates to the exceptionally good response of haematological indices to supplementation with iron alone. The response is clearly better than that obtained in other community-based trials.⁴ The differences might be due to several factors, but clearly the mode of supplementation and supervision in the trial implies a high level of compliance. The results of this trial should therefore be interpreted with respect to efficacy of the interventions in a scientific or explanatory trial, which might have quite different results from what would be the community effectiveness of a programme with these interventions, if it were ever implemented.

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Synergistic effects of pentoxifylline and dapsone in leucocytoclastic vasculitis

SIR—Cutaneous leucocytoclastic vasculitis (CLV) may be associated with several inflammatory, autoimmune, and malignant diseases. In cases where suspected aetiological factors such as drugs, infections, or neoplasms can be defined and removed, the disease can be treated effectively. However, when no stimulus is detected and avoidance or removal are not possible, there has been until now no good alternative therapy to systemic corticosteroids. Drugs such as dapsone or pentoxifylline (PTX) have been introduced in CLV with variable effects,¹⁻³ but there have been no reports of use of a combination of these drugs in vasculitis. We report the synergistic effects of combined therapy with dapsone and PTX in three patients with CLV.

A 40-year-old woman with chronic hypocomplementaemic urticarial vasculitis had been treated with dapsone or PTX with only minor improvement. She was then given PTX 1200 mg per day and dapsone 100 mg per day. After 2 weeks, her purpuric urticarial weals and signs of systemic manifestations (conjunctivitis, arthritis, and abdominal pain) had dramatically improved and disappeared completely after 6 weeks of continuous therapy. During the subsequent 16 months of treatment, no serious side-effects were observed.

A second patient with a bullous leucocytoclastic vasculitis associated with rheumatoid arthritis had been treated with several cytotoxic agents and dapsone with only limited results. Within 14 days of therapy with PTX and dapsone at the same doses for the previous patient, the vasculitic skin manifestations disappeared and arthritis improved. 4 weeks later, treatment with PTX had to be stopped because of severe headache that was refractory to analgesics.

A third patient with a leucocytoclastic vasculitis associated with Sjögren's syndrome was treated for 12 weeks, with total control of the cutaneous manifestations of her vasculitis, on

the PTX/dapsone combination. No adverse events were observed.

Formation of immune complexes followed by leucocyte activation and release of reactive oxygen metabolites has been implicated in leucocytoclastic vasculitis. Dapsone has been shown to affect various neutrophil functions such as myeloperoxidase-mediated iodination, lysosomal activity, generation of active oxygen metabolites, and chemotaxis.⁴ Dapsone inhibits neutrophil adherence mediated by integrins and suppresses cell attachment to basement-membrane-bound immunoglobulin A and immunoglobulin G.^{5,6} PTX is also capable of inhibiting basal and stimulated neutrophil adhesion to both aortic and pulmonary bovine endothelium, and it reduces the adhesion-promoting effects of complement components (C5a) and phorbol esters.⁷ In addition, suppressive effects selective for TNF- β production have been reported.⁸

These functions on activation and inflammatory activity of neutrophils may be the reason for the synergistic effects observed with dapsone and PTX. Since monotherapy has been reported to be of only limited effect, combined treatment with dapsone and PTX may offer new strategies in the therapy of refractory leucocytoclastic vasculitis, so avoiding side-effects of chronically administered corticosteroids.

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Prostate cancer

SIR—With respect to the report of a meeting of physicians and scientists of the Institute of Cancer Research and the Royal Marsden Hospital (Oct 9, p 901), since endocrine therapy is recognised as the almost exclusive treatment for advanced prostate cancer and is becoming part of therapy at earlier stages of the disease, two crucial points should be mentioned.

First, the adrenal glands are responsible for close to half the total androgens in adult men and not "a small extent" (as indicated on page 904 of that report). Second, as a logical consequence, combination therapy with a pure antiandrogen of the class of flutamide given in association with medical (luteinising hormone release hormone [LHRH] agonist) or surgical castration should be logically used to block simultaneously the androgens of both testicular and adrenal origins. This therapy prolongs the duration of response, and, most importantly, increases survival in all the reported prospective, randomised, placebo-controlled, and large-scale studies.¹⁻⁵

In fact, it should have been known at the time of that meeting at the Royal Marsden Hospital that the best results have been obtained in Europe by the European Organisation for Research and Treatment of Cancer (EORTC) in the clinical trial directed by Louis Denis, in which an advantage of 15.1 months of survival (52%) over control has been obtained in the group of men who received combination therapy with an LHRH agonist goserelin plus flutamide compared with orchiectomy and placebo when disease-specific causes of death were analysed. It should be recognised that a 52% increase in survival is a major success when compared with the prolongation of survival achieved in a somewhat similar disease, breast cancer, in which a 10–15% increase in survival is regarded as a satisfactory response and has led to the acceptance of tamoxifen as standard world-wide therapy. Why it is so difficult to recognise the clear advantages of a therapy for prostate cancer when similar or lower benefits are well accepted for any other type of cancer?

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Acquired transitory von Willebrand syndrome with ciprofloxacin

SIR—The acquired von Willebrand syndrome (AvWS) is a rare coagulopathy, usually associated with lymphoproliferative or myeloproliferative disorders.^{1,2} AvWS has been also frequently associated with valproic acid;³ no link with other drugs has been reported. We describe here two cases of severe and temporary AvWS, in whom ciprofloxacin was strongly suspected as the causal factor.

A 42-year-old man was referred in May, 1992, with abrupt onset of left abdominal wall pain and epistaxis. 15 days earlier he had had fever due to an ear infection and bronchitis. He had been prescribed deflazacort 15 mg per day and ciprofloxacin 250 mg twice daily for 7 days. The patient had had several bouts of coughing and complained of increasing discomfort in the left abdominal wall. Ultrasonography revealed a large haematoma of the left rectus muscle. No bleeding diathesis was evident in the family. All drugs were discontinued and his symptoms improved without resorting to blood products during follow-up.

A 32-year-old woman was referred in April, 1993, for profuse bleeding after dental curettage. One month before she had taken ciprofloxacin 250 mg four times daily for 2 days and miocamycin 600 mg daily for 4 days for infection of a congenital cyst of the chin. 10 days before admission she had profuse, short-lived bleeding after manipulation of an earring. Several attempts with tranexamic acid by mouth wash on 1 day failed to stop gum bleeding. Her haemoglobin fell from 13.6 g/dL to

| Test | At admission | After 1 mo | After 3 mo | After 5 mo |
|---------------------|--------------|------------|------------|------------|
| Patient 1 | | | | |
| Bleeding time (min) | 11 | 9 | ND | 4.5 |
| APTT (ratio) | 1.67 | 1.72 | ND | 1.05 |
| VIII:C (U/dL) | 8 | 9 | ND | 78 |
| vWF:Ag (U/dL) | 5 | 8 | 40 | 109 |
| RiCof (U/dL) | <3 | <3 | 35 | 88 |
| Patient 2 | | | | |
| Bleeding time (min) | >30 | >30 | 14 | 7* |
| APTT (ratio) | 1.16 | 1.10 | 1.00 | 0.94 |
| VIII:C (U/dL) | 45 | 60 | 74 | 88 |
| vWF:Ag (U/dL) | 22 | 26 | 43 | 91 |
| RiCof (U/dL) | 9 | 20 | 40 | 82 |

Normal ranges: bleeding time 3–7.5 min, VIII:C 51–147 U/dL, vWF:Ag 48–177 U/dL, and RiCof 50–187 U/dL. ND = not done.

*Obtained 8 months after admission.

Table: Coagulation studies and VIII/vWF indices at admission and during follow-up

10.2 g/dL 24 hours later. Intravenous desmopressin (0.3 µg/kg) stopped the bleeding, although the bleeding time remained prolonged (25 min), and the patient was discharged after another dose 12 hours later. No further bleeding episodes were observed during follow-up. No bleeding diathesis was evident in the family and the parents showed normal coagulation and von Willebrand factor indices (data not shown).

Coagulation assays at admission and during follow-up, assayed as previously reported,^{4,5} are shown in the table. In both patients there was a transient reduction in VIII/vWF measurements that was more pronounced in the first case. Bleeding time was substantially prolonged in the second patient, who had some evidence for dysfunctional vWF, as shown by the abnormal RiCof/vWF:Ag ratio (0.4 vs 0.98 [0.12] in 20 healthy controls), and the severely impaired ristocetin-induced platelet aggregation, present only at 2 mg/mL of ristocetin (controls 0.94 [0.18] mg/mL). Platelet aggregation with all other agonists was completely normal. Acquired factor VIII and vWF inhibitors were absent in both patients. Autoimmune disorders or monoclonal gammopathy was also ruled out. VIII/vWF indices returned to normal only 5 months later in both patients.

Ciprofloxacin has been associated with several adverse effects, possibly having a common immune-related aetiology. More recently, ciprofloxacin has been implicated in the appearance of an acquired factor VIII inhibitor in a haemophilia A patient.⁶ We think that in our patients there is a strong suggestion for a causal relation between ciprofloxacin and AvWS. To our knowledge, this is the first report of such an unusual association with sustained effect after discontinuation of the drug. Coagulation assays in patients on ciprofloxacin who develop bleeding seem advisable.

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