wide autoantibody and immune-complex production, including mixed cryoglobulins (3).

Our patient developed psoriatic lesions at the age of 32, and after 8 years migrant arthralgias. At the age of 51 he developed necrotic papular lesions and asthenia, and after 6 months a diagnosis of HCV infection was made, on the evidence of anti-HCV antibodies positivity. On admission to our department, physical examination revealed numerous erythematous papular nodular lesions and some ulcero-necrotic lesions, livaedo reticularis, a purplish mottling of the skin, and multiple psoriatic lesions. Laboratory findings showed ESR 75 mm/hr, AST 169 IU/l, ALT 147 IU/l; the presence of antibody anti-HCV was positive, detected by RIBA test. HCV-RNA test was positive, showing an active viral replication. Latex-agglutination test for rheumatoid factor was strongly positive. Serum immunoelectrophoresis revealed type III cryoglobulinaemia.

Because of the worsening of psoriatic lesions with the use of interferon alpha and the contraindication to the use of immunosuppressors and prednisone due to the active viral replication, we chose to use iloprost on the basis of the following considerations. Iloprost is a stable prostacyclin analogue, successfully used to treat Raynaud's phenomenon and digital ulcers associated with connective tissue diseases (4). The best known mechanisms of the drug action are vasodilation and antiplatelet effect, which have been demonstrated, may be involved in the exertion of its clinical efficacy but apart from these above-mentioned mechanisms, lymphocyte adhesion and IL-1 stimulated expression of ICAM-1 and ELAM-1 also exhibit a significant reduction in the presence of iloprost; moreover, this drug induces fibrinolysis, increasing in red cell deformability, inhibition of vascular smooth muscle cell proliferation, down-regulation of leukocyte adhesion molecules and the inhibition of lymphocyte production of proinflammatory cytokines, such as TNF-α, IL-1 and IL-6 (5). It has been furthermore demonstrated that prostacyclin or its stable analogue partially inhibits the adhesion of polymorphonuclear cells and lymphocytes to endothelial cells, and this has to be considered in the treatment of ischemic diseases whatever the aetiology is, since it is well-established that neutrophil adhesion to the endothelium plays a central role in ischemia-reperfusion injury (6). We therefore used i.v. iloprost 2 ng/kg/min, administered for 6 hours daily for 5 days. At the end of the treatment, a substantial improvement occurred (Fig. 1) with the disappearance of necrotizing lesions.

We conclude that the immune response to HCV and the cryoglobulins related to infection can lead to several clinical features, among which papular-nodular and ulcero-necrotic must be considered. In this case, but also in other kinds of coetaneous involvement, iloprost may be a useful tool when other therapies are not available, or as an adjunct to steroids and immunosuppressors.

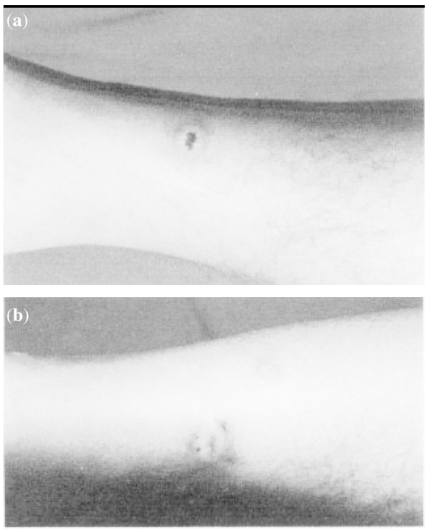

Fig. 1. Vasculitic lesions before (**a**) and after (**b**) treatment with iloprost.

R. LO GULLO, *PhD*
L. DE FILIPPIS, *MD*
A. CALIRI, *MD*
G. BAGNATO, *PhD*

Department of Rheumatology, Policlinico Universitario G. Martino, Messina, Italy.

Corresponding author: Luigi De Filippis, Policlinico Universitario G. Martino, 98100 Messina, Italy. E-mail lgdef@yahoo.it
Reprints will not be available from the author.

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A mistake in the history of aspirin

Sirs,

We would like to point out a widespread misapprehension in the rheumatological literature. In several histories of aspirin (1-4) two Italian chemists, Luigi Valentino Brugnatelli and Felice Fontana, are credited with the extraction of salicin from willow bark in 1826, two years earlier than Johann Andreas Buchner, Professor of Pharmacy in Munich, Germany (5). Brugnatelli and Fontana were eminent Italian chemists at the beginning of the 19th century: Brugnatelli was Professor of Chemistry at the University of Pavia and Fontana was the first Director of the Museum of Natural History in Florence, but neither of them conducted research on salicylic compounds. Furthermore, they both had passed away before 1826: Felice Fontana died in 1805 and Brugnatelli in 1818.

The first extraction of the active component of willow bark was actually performed in 1824, i.e. two years before the reported date, by two other Italian researchers, both of whom were pharmacists – Bartolomeo Rigatelli in Verona, and Francesco Fontana in Lazise, near Verona. Rigatelli named the drug "salino amarissimo antifebbrile" (bitter febrifugal saline), while Fontana utilized the same term – salicin – that a few years later was to be adopted by Buchner. Unlike Brugnatelli and Felice Fontana, they were not connected with academic world and they published the results of their studies in local journals (6, 7). This may explain the *quiproquo*, together with the assonance between Brugnatelli and Rigatelli and the homonymy between Felice and Francesco Fontana.

It was not easy to retrace the origin of the mistake. The earliest paper in the international literature in which we found a citation of Brugnatelli and Fontana was that by Julius Wohlgemuth in 1899 (8), but they had already been erroneously cited in 1845 by Raffaele Piria (9), another Italian chemist who in 1838 (10) was the first to isolate salicylic acid from salicin. Progess in any field is built of of many little stones and we are aware of the relatively trivial nature of this detail. Nevertheless, we think that is worthwhile to re-establish the truth and to recognize the merits.

P. MARSON[1], *MD*
G. PASERO[2], *MD*

[1]Unità di Emocitoaferesi, Servizio Immunotrasfusionale, Azienda Ospedaliera di Padova; [2]Department of Internal Medicine, U.O. di Reumatologia, University of Pisa, Italy.
Please address all correspondence to: Giampiero Pasero, MD, c/o Clinical and Experimental Rheumatology, Via Santa Maria 31, 56126 Pisa, Italy

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BCG as a new therapeutic and prophylactic agent in patients with severe oral aphthosis

Sirs,

Recurrent aphthosis (RAU) is a major public health problem that has been considered as the most frequent oral mucosal disease in children and adults, affecting 20-25% of the world population (1). Its etiopathogenesis is obscure although immunodysregulation has been proposed by several investigators (2-4). The therapy of this medical problem remains an important dilemma. Many therapeutic trials that have shown benefit in the relief of oral aphthosis of antibiotics, anti-inflammatory, immunomodulators, anesthetics and alternative (herbal) remedies (4).

BCG was introduced as a vaccine against TB (7), but in recent years it has also been found to act as an immunomodulator in cases of leprosy, as the incidence of this disease was reduced tremendously after introduction of the BCG vaccine (7). BCG has been used successfully in the treatment of alopecia areata (6). In addition, the incidence of skin disorders has been reported to be low in BCG-vaccinated subjects (6).

Thirty-six patients (22 males and 14 females, age range 14-55 yrs, mean 25 yrs) with classic severe oral aphthosis, who presented to the multi-disciplinary Behçet's clinic, were enrolled in this study. Patients with features of Behçet's disease and other related problems were excluded. The selection of patients was limited to those with multiple lesions for at least 7 days each month during the 6-month period preceding the study. Patients were assessed using an oral clinical manifestation index which was designed by our clinic (Table I).

All those patients were vaccinated with 0.1 ml BCG vaccine in the deltoid area of the left arm 3 times at one month intervals. Patients were evaluated every month during the 6-month period of treatment (3 months) and follow-up (3 months) using the OCMI. The data were analyzed and the results were compared with each other before, after treatment and during follow-up using the ANOVA test.

Thirty-six patients (22 male and 14 female, whose age range 14-55 years, mean 25 years) were enrolled in this study. The results of OCMI before, every month (3 months) during BCG vaccinations and follow-up month (three) were summarized in Fig. 1. The result of BCG was very encouraging as the OCMI was reduced after the second month and reached minimum after the third vaccine (mean 7.55) which was statistically significant with the P value at 0.000001. During follow-up improvement was promising as during therapy and, when the result was compared after three months of follow-up with the OCMI before therapy, it was also statistically significant.

Many studies are encouraging an immunological dysfunction theory in attiopathogenesis of RAS as the analysis of the peripheral T-lymphocytes in patients with aphthae shows a decreased ratio of T-helper ($CD4^+$) cells to T-suppressor/cytotoxic ($CD8^+$) and, furthermore when aphthae have been investigated locally in oral mucosa, an increased percentage of ($CD8^+$) cytotoxic cells have been seen (3, 4). BCG has been used in the last years as an immunomodulatory agent and has been found to be effective in the treatment of alopecia areata (6), malignant melanoma (6), viral warts (7), and diffuse cutaneous leishmaniasis (6) etc. The present work showed that BCG is effective in controlling aphthosis. This has been shown clearly during the second month and improvement continued even during the 3-month follow-up. This supports the idea that BCG has a therapeutic and prophylactic role in the management of oral aphthosis. Further follow-up is needed for further evaluation of this therapy.

The mechanism of the action of BCG in the treatment of oral aphthosis cannot be clearly explained but most probably it is through its immunomodulatory effect.

This BCG immunotherapy also has been tried in Behçet's disease and the preliminary result is encouraging (Sharquie and Hayani 2004, unpublished data). In conclusion, the BCG vaccine is an effective new mode of therapy in patients with oral aphthosis and further evaluation through double-blinded studies is indicated to overcome the bias effect of spontaneous remission.

K.E. SHARQUIE[1], *MD, Professor*
R.K. HAYANI[2], *MD*

[1]Department of Dermatology and Venereology, College of Medicine, Baghdad University, Baghdad, Iraq, E-mail:ksharquie@yahoo.co.uk;
[2]Department of Dermatology and Venereology, Baghdad Teaching Hospital, Baghdad, Iraq.

Table I. Clinical oral manifestation index.

Type	
Minor ulcer	1
Herpetiform	2
Major ulcer	3
Number / attack	
1-3	1
4-6	2
7-9	3
9-12	4
More than 12	5
Duration of the attack	
1-4 day	1
5-8 days	2
9-12 days	3
More than 12 days	4
Frequency (attack/date)	
0-2 weeks	5
3-4 weeks	4
5-6 weeks	3
7-8 weeks	2
More than 8 weeks	1
SX	
Uncomfortable	1
Painful not interfere with eating or swallowing	2
Interfere with solid feeding	3
Interfere with liquid eating	4

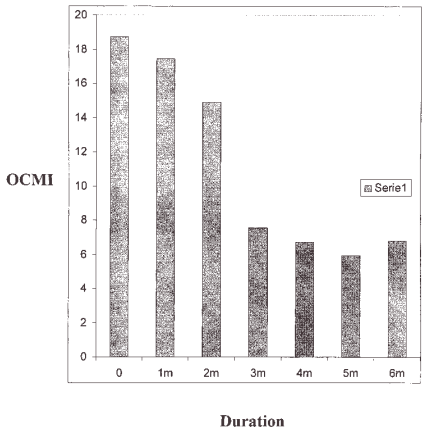

Fig. 1. Results.

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