

The New England Journal of Medicine

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NOTICES should be received not later than noon on Monday, 24 days before date of publication.

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SUBSCRIPTION PRICES: USA: \$30 per year (interns, residents \$23 per year; students \$18 per year). Canada: \$40 per year (interns, residents \$30.50 per year; students \$24 per year).

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THERAPEUTIC POTENTIAL OF TRANSFER FACTOR

THE ability of a low-molecular-weight material from sensitized lymphocytes to transfer cell-mediated immune responses to previously unreactive recipients was reported many years ago.¹ During the past decade, there have been several investigations into the possibility that this form of passive sensitization might be efficacious in patients with cancer, autoimmune diseases, immunodeficiency syndromes, or a variety of inflammatory disorders of uncertain origin. The reports have been promising but inconclusive; either too few patients were studied or the "transfer factor" was used in combination with other agents that may have produced similar results.

It is still too early to state that transfer factor is appropriate therapy for any of the above diseases. However, several recent reports suggest that the ability of the recipients of transfer factor to acquire and maintain appropriate cell-mediated immune responses may be an important determinant of the outcome of this form of treatment. For example, most patients with chronic mucocutaneous candidiasis do not respond to transfer factor unless they are simultaneously treated with antifungal antibiotics.² In addition, the long-term benefit of this combination therapy is most striking in patients who acquire cellular immunity to candida²; conversely, loss of this immunity may be followed by clinical relapses.³

Additional evidence for the importance of the recipient's immune potential has been presented by Ritts et al.⁴ in patients with osteogenic sarcoma. Their patients were classified as "converters" or "nonconverters" depending on changes in delayed cutaneous hypersensitivity after no more than three injections of transfer factor from donors who had been "cured" of osteogenic sarcoma for at least five years. The skin-test antigens were purified protein derivative, streptokinase-streptodornase, mumps, candida, and chloro-dinitrobenzene; specific tumor immunity was not studied. No converters received chemotherapy, but some nonconverters received methotrexate, vincristine, and doxorubicin. After a follow-up period of 24 months, 13 of the 15 converters (86 per cent) were alive, and only four (27 per cent) had metastatic cancer. In contrast, seven of the 15 nonconverters were dead, and 11 had metastases.

Also pertinent are the observations of Sharma et al.⁵ in cutaneous leishmaniasis. Their study was a double-blind comparison of the effects of placebo and transfer factors from two different sources. The donors of transfer factor either had histories of cutaneous leishmaniasis or resided outside an area where leishmaniasis was endemic and had no evidence of previous leishmaniasis infections. All other medications were withheld throughout the 12-week clinical trial. Ten of the 12 recipients of "leishmania-immune" transfer factor had healing of their lesions, but a similar healing effect was seen in only three of the 13

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recipients of "nonimmune" transfer factor. None of the placebo-treated patients had healing. Although the good responses observed in the recipients of non-immune transfer factor may indicate a nonspecific effect, it is noteworthy that these responses only occurred in the three patients who had positive tests for leishmania before they were treated.

Although these reports permit no conclusions concerning the efficacy of transfer factor, each provides evidence that the potential of the recipient for immunologic reactivity may be related to the outcome of transfer-factor therapy.

In this issue of the *Journal*, Steele and his associates present a novel study in which transfer factor was used to protect against varicella-zoster infections in children with leukemia. This clinical trial was derived from two previous studies. The first demonstrated that pretreatment with transfer factor protected marmosets from otherwise fatal infections with *Herpes simplex* virus but that the same preparations were ineffective in treatment of active infections.⁴ The second was a pilot study⁷ in which transfer factor induced cellular immunity, but not antibody production, to varicella-zoster antigens in patients with leukemia.

The results of the clinical trial are impressive. Sixteen recipients of transfer factor were exposed to varicella zoster, but only one had a clinical infection, and it was very mild. In contrast, 13 of the 15 members of the placebo group exposed to varicella zoster had clinical infections, and three were disseminated.

This report suggests that transfer factor may provide an alternative method for immunization against certain infections for which no effective vaccines are available. However, it does not help to resolve the lingering controversy over the specificity of the immunologic effects of transfer factor.⁸ It would be useful to know whether similar preparations from donors without cellular immunity to varicella zoster could provide protection for similar patients.

The mechanisms of this effect of transfer factor are unknown. The fact that cellular immunity to varicella-zoster antigens persisted for many months argues against a relatively short-lived and nonspecific event such as interferon production.^{9,10} Antibodies against varicella zoster were not detected unless the recipients were exposed to the infection, and antibody responses by the subjects treated with placebo and those treated with transfer factor were comparable. Thus, it is likely that the protective effect is mediated through immune functions such as cellular cytotoxic activity or production of soluble mediators,⁷ but this has not been established.

This important contribution should lead to additional controlled clinical trials. Investigators must also recall that treatment with transfer factor has had adverse effects.¹¹ Even though the relations between transfer-factor therapy, the underlying disease, and the adverse reactions are still unclear, we must be alert to the possibility of adverse effects if an immu-

nologically active agent is administered to patients with abnormal immune systems.

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CLINICAL USE OF A BLOOD SUBSTITUTE

To the Editor: We report here the first therapeutic use of an experimental, oxygen-transporting blood substitute, Fluosol-DA 20%. It is made and supplied by the Green Cross Corporation (1-47, Chuoh 1-chome, Joto-ku, Osaka, Japan), whose records confirm this case as its initial clinical use. Its active ingredients (perfluorodecalin and perfluorotripropylamine) give this biologically inert emulsion a high oxygen-carrying capacity of 7.2 volumes per volume at 37°C; the oxygen-carrying capacity of red cells is 17 to 20 volumes per volume. The safety and efficacy of Fluosol have been demonstrated in wide and comprehensive studies in animals, in decerebrate human subjects, and in normal human volunteers, as described elsewhere.¹⁻⁵ On the basis of these results, clinical study seemed warranted.

An appropriate occasion arose when a 65-year-old man was at risk for hemorrhagic shock due to massive bleeding from a gastric ulcer and so required emergency gastrectomy. The blood bank was