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Transfer Factor

For over a decade after its discovery[1] transfer factor was regarded as a laboratory curiosity, outside the mainstream of immunological research and of little relevance to clinical practice. Within the past five years it has achieved prominence not only in its role in cell-mediated immunity but also as a therapeutic agent justifying intensive clinical trials in a variety of diseases. Its immunological properties have now been repeatedly confirmed,[2] in particular its ability to confer on previously unresponsive recipients delayed hypersensitivity skin reactions to a variety of microbial antigens. The physical characteristics of transfer factor have also been delineated in some detail. It is not analogous to any known immunoglobulin class, nor is it itself immunogenic; and indeed its failure to conform with preconceived ideas of how a respectable mediator of immunological reactions should behave was largely responsible for the slow acceptance of its existence. Recent studies indicate[3] that transfer factor consists of a short polypeptide chain joined to three or four RNA bases. While it is far from proved that transfer factor is normally concerned in collaboration between T-lymphocytes and other lymphocyte populations in the induction of delayed hypersensitivity,[4] antibody synthesis,[5] or cytotoxic reactions against cells with viral, tumour specific or histocompatibility antigens,[6] doubts that these interactions, are normally mediated by immunoglobulins[7] have made immunologists more susceptible to other possibilities—in particular, that informational macromolecules such as nucleic acids may fulfil this role.

There is widespread support for the idea that, in a clinical setting, transfer factor activates recipients' lymphocytes so that a new line of antigen-specific cells is generated.[8] But these cells are almost certainly triggered to produce other products of activated lymphocytes, including interferon,[9] so some problems remain to be settled. One important question is the extent to which the active principle of transfer factor, as presently isolated, is contaminated with other biologically active mediators. The second question concerns the precision with which immunological reactivity can be conferred on recipient cells without exciting the irrelevant and possibly undesirable effects of non-specific stimulation.[10]

The clinical use of transfer factor is based on the theory that depressed cell-mediated immunity accounts for a variety of disease states and that by reversing this deficiency transfer factor can relieve the disease process. This view is easiest to accept for severe infections by identifiable mycobacteria, fungi, or viruses, particularly in patients with defects in lymphocyte responsiveness either in vitro or in vivo. Similarly, it is reasonable to attempt the correction of primary immunodeficiency diseases where there are abnormalities in lymphocyte function, though the chance of success must surely depend upon the presence of lymphocyte populations with which transfer factor can interact. Even when the basic abnormality cannot be corrected non-specific activation of existing lymphocyte populations may help to eradicate secondary infection.[10] There is less justification for the use of transfer factor in persistent virus infections such as subacute sclerosing panencephalitis,[11 12] in which patients have almost certainly already acquired vigorous cell-mediated immunity to the defective measles virus responsible for the disease.[13 14] Even in acute virus diseases the reported remissions[11] may be the consequence of interferon production,[9] so that transfer factor would be one only and not necessarily the most efficient means of controlling virus infection. Its most controversial application is in the treatment of neoplastic chronic inflammatory and demyelinating diseases. Here the cause of the disease is unknown, the role of immunological deficiency is hypothetical, and, as no causative micro-organism can be identified, there is less possibility of selecting specifically immune donors.

Several results of transfer factor treatment have already appeared. Among immune deficiency diseases, patients with Wiskott-Aldrich syndrome have reportedly benefited from repeated injections of transfer factor[15] with a reduction in severity of eczema, recurrent infections, and bleeding from thrombocytopenia. Results with other primary immune deficiency disease are less convincing,[16-18] but the place of such treatment in this group of diseases will be modified by the recognition of more subtle deficiencies in T-lymphocyte function using improved in vitro tests. Valdimarsson *et al.*[19] have recently described a 3-year-old girl with a hitherto unrecognized form of T-lymphocyte deficiency whose clinical and laboratory abnormalities responded to treatment with a dialysable leucocyte extract.

The infectious disease in which transfer factor has been most frequently reported to induce remissions is chronic mucocutaneous candidiasis.[20-23] Clinical improvement can be correlated with the specific repair of deficient cell-mediated immunity to this organism. Similarly coccidioidomycosis,[24] leprosy,[25] and some virus infections[11] have responded to

treatment with transfer factor obtained from donors with strongly positive skin tests to the relevant antigen. There are obvious difficulties in treating patients with diseases of unknown aetiology by this method, though on occasion experimental evidence allows the imaginative selection of donors. For example, a defect in cell-mediated immunity to measles antigen in patients with multiple sclerosis[26] can be corrected in vitro by transfer factor prepared from the lymphocytes of donors with strongly positive skin reactions to measles antigen,[27] suggesting that these cells are a suitable source of material for immunotherapy. Laboratory tests have also been used to prepare transfer factor for the treatment of osteogenic sarcoma,[28] the donor lymphocytes having shown vigorous inhibition of tumour cell growth in vitro.[29] Transfer factor has already been used in the treatment of melanomas[30] and carcinoma of the breast,[31] but its place in cancer immunotherapy is far from firmly established.

The possibility of treating chronic inflammatory diseases with transfer factor has also been widely debated[2] and encouraged by a growing appreciation that immune deficiency to viral or other microbial antigens may predispose to diseases such as, for example, glomerulonephritis.[32] While transfer factor did not help patients with rheumatoid arthritis,[33] remissions have been induced in Behçet's disease accompanied by vasculitis,[28 34] providing a possible explanation for the successes reported many years earlier with fresh blood transfusions.[35] Indeed, many unexplained therapeutic successes attributed to fresh blood transfusions may be attributable to transfer factor.[36]

Clearly, enough has already been done to justify controlled trials of transfer factor in a variety of diseases. With rare diseases such as the Wiskott-Aldrich syndrome this may not be practicable, but with common conditions such as rheumatoid arthritis such an approach is indispensable. As with any biological preparation, some attempt at standardizing the injected material is mandatory. This includes a precise appraisal of the immunological reactivity of the donors and an in vitro assay of the potency of the lymphocyte dialysate. The latter procedure is now practicable[37 38] and should guard failures from injecting inactive material.[38] Previous therapy with other drugs may vitiate this treatment.[39]

Fortunately risks from hazards such as transmitting hepatitis virus appear negligible.[2] There is, however, a risk of exciting generalized hypersensitivity reactions to disseminated microbial or other antigens[40] and, paradoxically, treatment regimens may need to incorporate steroids or other anti-inflammatory drugs during their early stages. In immune deficiency states there is a hint that uncontrolled lymphoid cell proliferation[41] and even autoimmune disease may be additional complications.[41 42] Transfer factor justifies careful, critical study, but beyond that we should not yet be prepared to go.

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Finance and the Health Service

If Mrs. Castle were to ask the Department of Health's psychological advisers about the effects on behaviour of chronic anxiety, she would be told that they include depression, irritability, impatience, and reluctance to listen to reasoned argument. She would then need to look no further for the explanation of the root causes of three events of the past week: the report[1] on the ill-treatment of patients at South Ockendon Hospital, the ultimatum[2] from the nurses threatening resignation from the Health Service, and the dispute between the B.M.A. and the H.C.S.A. in the industrial court (p. 455). All reflect the behaviour of doctors and nurses driven to the end of their tether by the financial starvation of the N.H.S. as a whole and by their own declining incomes.

The inquiry at South Ockendon is the latest in a series of investigations of deaths, ill-treatment, and other abuses of patients in long-stay mental hospitals.[3 5] At least this time both the report and the Secretary of State have acknowledged that staff at the hospital were working in impossibly difficult conditions of overcrowding and lack of nurses. Each time such a scandal occurs there are demands from the press and assurances from the Government that more resources will be made available for mental handicap and other long-stay units—and it is true that some improvements have been made since the events that precipitated the inquiry. The main problem