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Transfer Factor As A Therapeutic Agent In Moderate And Severe Atopic Dermatitis

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The current knowledge of Transfer Factor (TF) actions as led immune response modulator has lead us to investigate its usefulness in-patients with atopic dermatitis. These patients that are unresponsive to the conventional therapy, show a cellular immune deficiency so that we believe possible to obtain a clinical improvement with the use of TF. We did a prospective, comparative, experimental study with 30 patients with moderate to severe atopic dermatitis (AD). Laboratory examination was performed in all patients: complete blood cell count, IgA, GM and E determination, lymphocyte subpopulations CD3, CD4, CD8, CD4/CD8 ratio, CD25, rosette formation for B and T Lymphocytes, coproparasitoscopic examination, throat and nose cultures, nasal cytology, skin test of cellular immunity to PPD, thrichophytin, candidine, varidasa, skin prick test to pollens, fungi, inhalants and foods. All patients underwent a sign and symptoms grading score system as follows: the parameters were erythema, pruritus, eczema, papules scored on a scale form 4+ to 0:0= no symptoms, + mild, ++= Moderate, +++= Severe, ++++= Very Severe. Initially all patients received one placebo unit every 15 days orally 3 times, then one after 30 days. Laboratory examination was performed and then treatment with transfer factor was initiated, 1 unit every 15 days three times and the fourth 30 days after. 15 days after the last dose a new immunological evaluation was done. Results showed a decrease in CD4, eosinophils and IgE, although not statistically significant. There was a statistically significant improvement in the 4 clinical parameters: erythema, eczema, pruritus and papules.

Treatment Of Atopic Dermatitis With Transfer Factor And Cyclosporin A

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Atopic dermatitis (AD) is a chronic skin disease that appears in patients with a personal or family history of allergic asthma and rhinitis. It is associated to the specific activation of a gene group. In most instances, the response to the conventional treatment is adequate. There are cases, though, known as refractory, where that is not the case. The study of two therapeutic alternatives, Transfer Factor (TF) and Cyclosporin A (CyA), was elaborated for this type of patients. AD patients were randomly divided in two groups. The first one was subjected to TF, as follows: one unit (U) every third day for the first week, 2U/week for the next three weeks and 1U/monthly to complete six months. Initial and final clinical and immunological testing was performed on both groups (eosinophils (EO), total IgE, CD4 and CD8). Six patients were included in group A and 12 in B. Both groups showed a significant statistical reduction in the total EO counts, without a statistical difference between them. None showed changes in total IgE levels. CyA reduced the CD4 counts, while TF increased the CD8 ones. Both with a p 0.05. Both groups showed clinical improvement statistical significant, but no difference between them were observed. Tolerance to the treatment was adequate, and there was no need to suspend the treatment in any case. Only three patients showed therapeutic benefits in the treatment of patients with severe refractory AD, with similar immunological improvement. Both drugs have different mechanisms of action, so their joint application probably could offer clinical benefits to the patients (synergistic action), cost reduction, and long-term treatment with reduced adverse effects.

Successful Treatment Of Posherpetica Neuritis (Caused By Herpes Zoster) With Specific Transfer Factor

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Neuritis posherpetica is one of the most important complications associated with Herpes zoster infection. It is characterized by intense pain that prevents patients from carrying out their normal activities. Our group has successfully treated a large number of Herpes zoster patients (together with the Cuban group more than 2,000) with specific Transfer Factor. We are now presenting the results of treating one of the Herpes zoster complications for which there has been no effective treatment available. The Transfer Factor was obtained from the Blood Bank, form healthy donors who as children has varicella (chickenpox). A group of 40 patients diagnosed with Neuritis Posherpetica were treated with Transfer factor (TF). The ages of patients varied from 32 to 65 years of age. The time of previous evolution of the infection was from 75 days to 7 years.

All patients have been previously treated with antiviral agents (90% with acyclovir), analgesics, vitamin B12 and carbamazepine (70% of the cases). The patients studied were selected for the presence of persistent neurosis. Before the study a "profile of cellular immune response" was performed and the common denominator was found to be a reduction in the percentage of T lymphocytes measured by rosette formation. The value of this immunological parameter was below normal values. The same was found for the intradermal reactions to PPD, candida, tricophytin and varidase. The treatment scheme with TF was 1 unit daily for 5 days, then 2 units a week (for 1 month), then 1 unit a week (for 1 month), in some of the patients the treatment was improvement in symptoms was noted for all patients. For ethical considerations treatment with carbamazepin and analgesics was continued in some of the patients. It may be concluded from this first study that TF is a valuable resource for the treatment and prognosis of this type of chronic ailment.

Suppurative Adenopathy By Salmonella B Treated With Transfer Factor

A Case Report

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A 6 year old, male, native from Toluca (Mexico), with past family history a dead brother 6 years old, with the same clinical characteristics. The patients main complain were: intermittent fever, giant adenopathies cervical, and then acquired fistulous section and purulent drainage of these adenopathies lasting two years of evolution. The patient received treatment for tuberculosis without response. One year later the patient was hospitalized again at the National Institute of Pediatrics (Mexico) with chicken pox and exacerbation of the symptoms.

Laboratory examination showed that haematological & usual urine, hepatic and renal functional tests were normal. Immunoglobulins, Complement and phagocytosis test and NBT reduction were normal. The febrile reactions reported: Tiphy 0=1:400, Paratiphy B=1:800, Paratiphy A=1:320. Specific antibodies for Salmonella B=1:320,000. The Cultures of Blood, feces and secretion of the cervical adenopathies were positive for Salmonella B. The Ziehl Nielssen in urine and secretion of the adenopathies were negative. The Ganglion Biopsy report: Lymphoreticular hyperplasia. With this clinical and laboratory picture a treatment with antibiotics was started and continued for ten days. However, the symptomatology continued, and the decision to begin "unspecific" Transfer Factor was taken, with partial response; later the administration of Specific Transfer Factor obtained through the immunization of a patients uncle, a complete remission of the symptoms was observed.

A defect in the cellular specific immunity was hypothesised, supported by the exacerbation of the symptoms with concomitant varicella manifestation. The initial decision was to start unspecific transfer factor and then because of the persistence of the symptoms, the pathogen specific transfer factor was given with the complete remission of the symptomatology, without relapsing after ten years of follow-up. This case can be considered as a defect in the specific cellular immunity for the Salmonella B antigens, because the patient showed a good response for other pathogens. We propose that a cellular defect in the differentiation of the T helper lymphocyte exists with a decreased TH1, that is critical for the production of IL2 and IFN gamma. In this patient, the excellent response observed with specific transfer factor supports this hypothesis.

Biological And Clinical Testing Of Swine Transfer Factor For Oral Administration (Imunorr)

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Dept. of Immunology of the Public Health Inst. has been involved in oral immunomodulation since the 80«s. In the years 1987-1988 laboratory reparation of swine transfer factor (TF) was started and later (1992-1993) a preclinical and pilot study of clinical testing of swine transfer factor for oral use was carried out. One unit of TF is dialyzable extract from $5x10^8$ peripheral blood leukocytes from a veterinary examined swine without any vaccination. Preclinical biological testing of TF was done on an inbred strains mouse model in several systems. The most important ones were: 1.- ex vivo/in vitro system: of experimentally immunosuppression (induced by Azathioprine) and following restoring effect of TF on in vitro mitogenic (PHA, ConA, LPS, PWM) proliferation of CD3, 4, 8 expression on peripheral blood lymphocytes (PBL), 2.- in vitro: proliferation of PBL induced with suboptimum ConA conc. (testing of constimulatory activity of TFp.o.), 3.- in vivo system: the host resistance against tumor growth (mouse leukemia cell line L1210). In all the above mentioned systems swine TF was compared with standard human TF preparation for injection (IMMODINR, Sevac, a.s., Prague). The general outcome of these tests was that oral TF showed equal or even slightly better significant influence on examined parameters when it was used in 5 times the dose used for injection. This result corresponds with published data.

A pilot clinical trial: 37 patients characterized predominantly by secondary immunodeficiency state, were treated only with oral TF for 6-10 weeks (one unit per weekly). The laboratory tests for T cell immunity parameters were done before and after treatment. It was shown a significant improvement of the several laboratory parameters (e.g. increase of CD3 and CD4 lymphocytes, active ERFC) ; significant clinical benefit was achieved when parameters of T cell immunity were decreased before treatment.

Transfer Factor (Immodin Sevac) Treatment Of Recurrent Anterior Uveitis.

A Retrospective Evaluation After 10 Years.

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Since 1987 an attempt to treat recurrent anterior uveitis by long-term application of transfer factor has been undertaken with the goal to reduce or possibly totally eliminate recurrent attack of this eye disease. Altogether, 50 patients at several time points have been enrolled into the study who, prior to the start of the transfer factor therapy, had had several attacks of uveitis per year, usually three or more. A commercial preparation of human transfer factor (Immodin SEVAC, Prague, Czechia) was used, applied normally at three months intervals by subcutaneous injection. The patients were subject to regular check-up at the Ophthalmology Dept. of the University Hospital: frequencies of recurrences of uveitis were recorded and compared to frequencies prior to the start of the treatment. The duration of treatment ranged from 35 to 85 months, the observation period was extended to 4 years after the therapy was completed; the longest observation period was more than 10 years. The final evaluation was based on hospital records and on simultaneous questioning the patients. Only a part of the 50 patients were lost from the final evaluation due to change of address or death.

The Transfer Factor treatment produced remarkably good results since of the 36 evaluated patients more than 70% experienced no typical recurrence at all. In about 25% of these patients some very slight eye discomfort was noted, (no more than 3-5 days of duration), that couldn't be compared to the severity of preceding attacks. Typical recurrences, usually in sporadic numbers, were observed in only a few patients who obviously did not respond well to the therapy. In conclusion, vast majority of the evaluated patients have been relieved from recurrent and severe attacks of uveitis even in the period after the application of the transfer factor had been finished.

Fifteen Years Of Clinical Use Of Dle-Immodin In Czech Rep.

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At our institute the research of TF-DLE started in 1967. At first we prepared and tested in laboratory experiments specific transfer factors. Biological activities of DEL from human and animal leukocytes (blood and lymphatic organs, bovine colostrum) were tested. Various methods of DLE preparation (disintegration of cells, ultrafiltration, dialysis) were tested as well. The low M.W. fraction is now produced by dialysis, ultrafiltration, pasteurized for 10 hours at 60iC and freeze-dried. Large clinical screening on more than 1.000 patients in 1982 was performed. Since then, more than 300.000 doses have been administered for therapeutic purposes. Some data on biological activities we have tested as well as a list of clinical effects attained with this preparation during its 15 years application are presented.

Efficacy Of Transfer Factor In Severely Infected Pediatric Patients

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Patients. This is a retrospective study of 45 patients treated from 1986 to 1998. These children were 3 to 16 years of age with an average of 4.2 years, severely infective and non-responsive to conventional treatment. Some had multiple infections. Twenty eight were girls, and 17 boys. They had: pneumonia (32 cases), gastrointestinal infections (8), repetitive urinary tract infections (12), vulvovaginitis (3), skin infections (11), herpes simplex I and II (5), osteomyelitis (1), undetermined fevers (8), malnutrition grade III (2), IgA deficiency (5), and IgG deficiency (1).

Methods. The patients were evaluated when they had already received conventional medication and their serological studies were available along with appropriate skin tests. The blood and serologic studies included: RBC sedimentation, C reactive protein, antistreptolysinase, febrile reactions, IgA, IgE, IgG & IgM, C3 & C4 components of complement, T&B lymphocytes, inhibition factor for lymphocytes migration to different antigens like candida, varidase, PPD & coccidiomycoides. However, their response rapidly worsened. The quantification of T lymphocytes was carried out and the percent of defective cells computed. The number of doses of the transfer factor programmed depended on this percentage. It was applied i.m. at 3-24 months. Control studies of the treatment were conducted. The clinical response was highly satisfactory, and all cases except 2 reached remission. These 2 cases had congenital deficiency IgA and IgG continuing with respiratory and digestive problems, but with improved performance.

Conclusion. We consider that the use of the transfer factor in these patients was a most useful application that allowed clinical and serological improvements, abated infections, shortened hospitalisation, and improved the quality of life.

The Transfer Factor In The Management Of A Case Of Encephalitis Caused By *Coccidioides Immitis.* A Case Report.

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This Case was a boy of 5 from Gomez Palacio, Durango with clinical meningitis. Cerebrospinal fluid cultures were positive for *Coccidioides immitis*. The condition was treated for 112 days with iv and intratecal Amphotericin B and Fluconazol without favorable response. A ventriculoperitoneal tube for hydrocephalia was installed without neurological improvement. T lymphocytes were at 32% with control at 50%. Migration inhibition and intradermal tests were negative for coccidioidin.

A regime of 29 doses of transfer factor i.m. gave satisfactory clinical results with remission of the neurological problem, disappearance of fever, T cell increase to 58% with 64% for the control. MIF to coccidioidin continued negative and the intradermal reaction to cocci produced only erythema. CFS became negative. The patient resumed normal activities.

Comment. The specific cellular defect in this patient with coccidiomycosis was established by quantification of T lymphocytes. There was a defect of 36% with absence of intardermal response to coccidioidin with MIF 0. Following the lack to response to conventional therapy, specific transfer factor permitted clinical improvement. However, in laboratory tests, the patient did not become positive for either test with coccidioidin.

Management Of Hypereosinophilia With Transfer Factor

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The patient was a girl of 2 from Cd. Frontera, Coahuila, hospitalised following high temperature (up to 38.5iC) for 6 months with general malaise, loss of 2 kg, non-responsive generalized dermatitis classified as scabies, and basal pneumonia. Paraclinical studies showed 6.5 g hemoglobin, hypochromia, anisocytosis, leukocytosis to 55900, 87% eosinophilia with 48633 eosinophils, 2900 IU IgE, 2130 mg% IgG, 38% T lymphocytes with control at 54% and 17% B lymphocytes.

The patient was studied under the protocol of hypereosinophilic syndrome, dismissing hypotheses such as neoplasms or parasitoses. Twenty-seven doses of transfer factor were used to manage this defective cellular immunity. Satisfactory recovery included normal growth, normal temperature, remission of skin lesions, normal coloration of membranes, adequate haemoglobin at 12.1 g, drop in leukocytosis to 7700 with eosinophils at 1309, and IgE dropped to 452 IU. The patient became asymptomatic.

Comment. This patient had a cellular defect shown by T cell counts at 30% defective. At the time the study was carried out TH1/TH2 was not assessed, although it would have helped in establishing the imbalance. However, we think that there was a TH2 defect that generated the eosinophilia and hyper IgE. This defect was controlled by the administration of transfer factor.

Use Of Transfer Factor In A Case Of Refractive Urinary Tract Infection

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This patient was a girl of 5 with persistent urinary tract infections from 5 months of age with malaise and fever whose urocultures were positive for *Escherichia coli*. Growth retardation included 8.3 kg & 88 cm at 1 year, 10 months, and 10.0 kg and 88 cm at 2 years, 10 months. Radiologically, there was a reflux of vesicoureter II. T lymphocytes were 9% of a control at 48% defective at 81.5%. by the migratory inhibition test for varidase, was negative and with PPD at 10%. A total of 82 doses of transfer factor were applied im. At the 6th dose, urocultures were negative. At the final treatment, T lymphocytes were at 43% as the normal reading was with the migratory test for varidase 25% and for PPD 33%. Later she had a urethral reimplant with satisfactory results. A year later she had negative urocultures no fever and good body growth.

Experience With Transfer Factor in 60 ICU Patients.

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We present preliminary clinical data using Transfer Factor in 60 ICU patients. Patients were divided in two groups: Group A- Patients hospitalized but not critically ill, and Group B- Patients in ICU. Our study is observational, since for many patients it was impossible for us to perform an experimental double blind prospective study.

Criteria were: -Patients with immunodeficiencies and diabetic patients unresponsive to conventional therapy.

Although at the beginning of the study we intended to determine several cytological and immunological parameters, obtention of data was too slow to be useful for clinical decisions. In all cases, 1 vial of Transfer Factor was used 3 times a day for 3 days via oral, IM and IV, depending on patient and physician preference.

Results. In all cases, there was a clinical improvement , impossible to obtain otherwise. We also noticed a better resistance of the patients to surgery, fewer complications, etc. As a consequence, there was a reduction in the hospitalization time.

Conclusion. This is not a controlled study, but our observations suggest the possibility of clinical use of Transfer Factor in the type of patients we studied. We believe that a controlled clinical trial should show the usefulness of Transfer Factor in critically ill patients.

TF, Psoriasis And Cytokines

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Psoriasis is characterized in histopathology by infiltration of leukocytes, hyper-proliferation of epidermal keratinocytes and the shorten cell renewing process. More and more, in the studies of psoriasis, the results have showed that cytokine system possessed important role in the network of inflammatory pathogenesis. It might be significant to inhibit the synthesis of specific cytokines or block the combination of activation of those receptors in therapeutics. Therefore, we started the clinical observation on 38 psoriasis patients with the treatment of Oral Transfer Factor (OTF) and the basic study on the mRNA expression of related cytokines (IL-8, IFNr, TNF:ç) within the skin lesions before and after the treatment.

The results indicate that skin inflammation was improved and the mRNA expression of IL-8, IFNr and TNF were reduced obviously. Furthermore, this suggests the role that such cytokines may play in the pathogenesis and therapy of psoriasis.

Clinical Study Of P-TFOL Liquid Treating Hepatitis

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PURPOSE: To evaluate the therapeutic effectiveness of P-TFOL produced by Jiang Xi Gannan Pharmaceutical Factory in treating hepatitis B.

METHODS: 25 hepatitis B patients have been studied ages 16-67 (mean 39.2), hepatitis B history1~20 years (mean 6.48), 17 of them are men. Every patient drinks P-TFOL 10 mg (10ml) per day for 3 months. Liver and kidney function, serological and virological test have been done before and after treatment.

RESULTS: (1) P-TFOL can improve some symptoms. (2) It can decrease serum transaminoferase in 56% patients, but albumin and bilirubin can not be changed. (3) It can affect hepatitis B virus (HBV) serology, HBsAg disappeared in 1 of 25 patients, 2 HBV-DNA became negative in 14 patients with both HBeAg and HBV-DNA positive, one HBeAg became negative, HBV-DNA became negative in 8/9 (88%) with both HBeAg-negative and HBV-DNA positive patients, ALT decrease in the same time. (4) It can prominently improve T-cell subtypes, CD4 became normal in 84% (11/13) and CD4/CD8 ratio increase in 61% patients. (5) In all patients, P-TFOL has therapeutic effectiveness in 52% patients, 3 of them are prominent and 12 of them are invalid. All these results suggest that P-TFOL can play a role in regulation of immunological system, it can improve hepatitis B patientsÕ immunological function, protect liver and inhibit HBV replication. It is worth being used as an adjuvant treatment of hepatitis B.

Observation Of 26 Senile Cases Treated With P-Tfol

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At present, the study of senility shows there are lots of harmful factors in the body that can result in senility. Researchers also found that the decrepit of the immunity function is one of the most obvious features of senility and it shows itself mainly in the decrepit of the cell immunity. The help/inducer T cell and cytotoxic/suppressor T cell take important roles in the adjustment of response to immunization in body. We use random sampling method to observe the T lymphocyte subpopulation of 26 aged people who take the P-Transfer Factor Oral Liquid (P-TFOL) produced by Jiang Xi Ganna Pharmaceutical Factory. Three months they took the P-TFOL, the CD8 decreased. Processed by statistics, our results prove to be meaningful.

Therapeutic Trial Of Antigen-Specific Transfer Factors In The Chronic Fatigue Immune Dysregulation Syndrome: Evidence Of Latent Virus

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Antien-specific Transfer Factors (ASTFs) were used serially in blind "placebo" controlled crossover study of 40 patients with Chronic Fatigue Immune Dysregulation Syndrome (CFIDS), so severely ill that they were unable to work for 2-10 years and unable to leave their house or even their room. Of the 40 patients, clinical improvement occurred in 32 with one of the five ASTFs, generally within 3-6 weeks of beginning therapy and was dramatic at 3 months. Antigen-selective defects in Cell-Mediated Immunity (CMI) to one or another virus corresponded with clinical response to the relevant TF but not to control TF (HHV1-TF). Some patients with defective CMI for CMV did not respond to HHV6-TF but responded to CMV-TF, and some with CFIDS due to the Rubella vaccine virus (5pts) responded neither to HHV6-TF, CMV-TF, nor EBV-TF but responded to the Rubella virus vaccine-TF. Two additional patients with past histories of severe hepatitis B, completely recovered by 1 ½-2 years prior to the onset of symptoms of CFIDS, did not respond to any of the three ASTFs used in the other patients, but did respond to ASTFs specific for Hepatitis B. In general antibody titers to the organism to which the TF was effective showed an inverse correlation with CMI.

Opportunities For Clinical Trials With Transfer Factor

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It is important to have an agreement as to the criteria for developing clinical studies with transfer factor (TF) and to discuss how best to document effectiveness of specific preparations. Despite the publication of numerous reports demonstrating the efficacy of TF in a variety of disorders, the scientific community remains skeptical in regard to its potential in clinical medicine. A series of collaborative studies with Drs. Dimitri Viza and Giancarlo Pizza have shown that effective TF produced in vitro and replicated in standardized reproducible batches can be safely used in clinical trials. Therefore, the possibility for replicating studies with TF in multiple centers is now an achievable goal that can lead to greater acceptability of this material in absence of complete biochemical characterization. Several criteria are needed for the initiation of clinical trials: 1) The problem should be an important medical issue; 2) There should be the opportunity for short-term objective documentation of effectiveness of the TF; 3) The study should be placebo controlled and double blind. We suggest initiating studies involving treatment of specific infectious agents where their control can be readily documented by collaborating laboratories. Among the most important current medical problems involving infectious agents are the following: 1) human herpes virus-induced Kaposi's sarcoma; 2) Epstein-Barr virus-induced malignancies, including AIDS-related central nervous system lymphoma, nasopharyngeal carcinoma and Burkitt's lymphoma; 3) cytomegalovirus-induced retinitis, and 4) human herpesvirus-6 pneumonia and encephalitis in immunosuppressed individuals. In spite of the changing pattern of HIV infection in developed countries with effective use of drug therapy, the complications remain a problem in developing countries as well as in individuals everywhere who develop drug intolerance or drug resistance. We will propose the details of possible multi-center trials of transfer factor with proven and documented effectiveness which will determine whether or not they can be effective in the treatment of the important clinical problems.

The Effect Of Transfer Factor On The Synthesis Of Human Cytokines

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Because TF contains approximately 200 different substances, fundamental information concerning its characteristics, such as the mechanisms of its activity, has been generated at a slow peace.

In this work, we show the development of an *in vitro* method for the evaluation of the effects of TF preparations, which were prepared at our school. 2x105 peripheral blood mononuclear cells (PBMC) were taken from healthy donors, then seeded in 96 well U-bottomed plates and stimulated in triplicate with TF, either concentrated or diluted 1:10 and 1:100. As an activation control ConA (10 ug/ml) was used and all the cultures were incubated for 6 h. Following incubation the cells were resuspended in lysis buffer. Subsequently, mRNA was analyzed by the RT-PCCR technique, using primers for B-actin, IFNy, RANTES, TNFx, IL-2 and osteopontin (OPN). The results show that only OPN mRNA is completely blocked in cells treated with TF, in a dose dependent manner.

Using ELISA kits we proved the capacity of TF to induce IL-8 and RANTES IN TF activated PBMC as well as in PMBC activated with supernatants derived from TF activated cells. We also investigated whether TF itself contains cytokines. None of the cases studied produced IL-8. A weak production of RANTES was observed in the PBMC cultures activated with supernatant derived from TF has a direct effect on PBMC and that indirectly may induce the synthesis of RANTES.

Dialyzable Lymphocyte Extracts Modify Soluble-Hla And Serum Lymphokine Levels

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Rationale. Soluble HLA class I antigens (sHLA) levels markedly increase during the course of viral infections, and we have shown that TF treatment also increases their serum level as it does that of certain lymphokines viz. IL-2 and IL-6. Thus, we have further investigated the variation of sHLA, in patients receiving TF treatment.

Methods. 41 patients suffering from recurrent ocular pathologies (keratitis, keratouvetitis, uveitis), were treated with LDV/7-produced-TF specific for HSV-1/2, CMV and EBV. Serum samples were collected and the sHLA level was determined by ELISA. In several of these patients the serum levels of MIF, RANTES, IL-4, IL-12, IL-15, and gamma-IFN were also tested.

Results. TF administration significantly increased the sHLA level in 25/41 patients ($P<0.008$). (Seven patients had an increase of >2SD and 14 of >1SD of the average range). Furthermore it was noticed a significant increase of MIF ($P<0.03$) and a near to significance one for IL-12 ($P<0.09$), gamma-IFN and Rantes. A significant decrease was observed for IL-15 ($P>0.05$) and a not significant one for IL-4. A statistical treatment of the data observed (Pearson correlations) suggests a direct correlation between HLAs and IL_12 ($P<0.026$), IL-4 and gamma-IFN ($P<0.001$) and an inverse correlation between IL-4 AND IL-12 ($P<0.030$) or Rantes ($P<0.01$). Also an inverse correlation was observed for gamma-IFN and MIF ($P<0.01$) or IL12 ($P<0.0001$). With a non-parametric evaluation (Spearman rank order correlations) a direct positive correlation between MIF and gamma-IFN ($P<0.05$) was also found.

Conclusion. Although preliminary, the present data clearly show the ability of DEL to modify HLAs and cytokines patterns in the patient's serum. The significance of these observations remains at present unclear. Nonetheless, they do confirm that the observed clinical activity of the TF administration is not due to a placebo effect but it is rather mediated by a complex interplay between cytokines and effector cells.

Cytokine And Lymphocyte Levels In Extrinsic Asthma Patients Treated With Transfer Factor

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In Bronchial extrinsic asthma inflammation has an important role in pathogenesis. We have measured cytokines and lymphocytes in patients with bronchial extrinsic asthma before and after treatment with Transfer Factor (TF).

Placebo (P) and TF were given to all patients for a six period each. During the treatment, cough, wheezing and sputum were clinically evaluated, as well as lymphocyte subpopulations, the later by flow cytometry. Cytokines were measured by ELISA.

CD4 lymphocytes were slightly increased before treatment, and remained so after P treatment. CD8, CD2 and B lymphocytes were within normal ranges, and did not show changes after TF treatment. On the other hand eosinophil counts decreased after TF treatment. TNF-a, IL-6, IL-8 and IL-10 were evaluated. We did not find TNF-a in patients sera, IL-6 levels were slightly increased ($p=0.052$); IL-8 levels were also increased, and did not show any changes after treatment ($p=0.02$). There were no changes in IL-10 levels. Regarding the clinical symptoms there were impressive results: coughing was reduced in 25% with P treatment vs. 60% with TF, wheezing was reduced by 30% with P treatment Vs. 80% with TF and sputum secretion was decreased only by 30% in P treated patients vs. 80% with TF.

Patients under TF showed clear clinical improvement (69.6%), but only had minor changes in lymphocyte sub-populations and cytokine levels.

Enhancing Effect Of Transfer Factors On Granulocyte-Macrophage Colony Forming Units Of Immune-Mediated Aplastic Anemia In Vitro

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The effect of transfer factors (TF) on colony forming units (CFU-C) of peripheral blood cells from patients with immune-mediated aplastic anemia (IMAA) was studied in vitro. TF were prepared following Lawerence's technique from leuko-concentrates of normalblood donors. Mononuclear cells form patients were incubated with or without TF in RPMI medium at a 5:1 ratio of TF: patients' lymphocytes at 37° C with a CO2 flow of 5%. Normal controls with and without TF were also incubated. The cells were then cultured in soft agar for 14 days. Besides, normal cells were cultured with the supernatants from the patient's cells. The cells of the patients incubated with TF showed a fifteen-fold increase in the numbers of CFU-c compared with those incubated without TF. Normal controls showed no changes with or without TF. However, when added the supernatants of the incubated cells of the aplastic patients, there was a significant decrease in the number of CFU-c (up to 10-fold). The decrease was much less striking with the supernatants of the aplastic patients incubated with TF. These results support the hypothesis that TF might correct the suppression of hemopoiesis in IMAA.

DLE Increase Stimulatory Effect Of Cytokines On Hematopoiesis

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Dialyzable extract of human leukocytes (DLE-Transfer f. IMMODIN SEVAC) belongs to BRM enhancing in vitro the effect of cytokines on differentiation and proliferation of progenitors of granulocyte and macrophage colony forming cells (GM-CFC) of the mouse BM. A single DLE injection to mice after sublethal gamma irradiation increased the recovery of GM progenitors as compared with controls and this stimulatory effect of DLE was further enhanced by repeated injections. Serum of mice treated with DLE has no CS activity in vitro but potentiates the effect of mouse CST as well as human rhu G-CSF on the growth of GM colonies from GM-CFC in mouse BM. Therapy with irradiated mice with rhu G-CSF enhanced the recovery of damaged progenitors in BM. Combined therapy of rhu-G-CSF and DEL elevated further this recovery. This therapy is now tested in patients with severe neutropenia.

Transfer Factor For Cell-Mediated Immune Response Rehabilitation Activities In Irradiated Mice

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The purpose of this investigation was to study the activity of TF preparations on the effect of radiation at doses that do not change hematopoiesis. Mice of Balb/c line were used. The animals were irradiated in doses of 0,5 and 2 Gy. TF preparations were studied for their: a) biochemical properties (presence of aminoacids, proteins, saccharides, nucleotides, nucleic acids); b) pharmacological characteristics (pyrogenity, toxicity, sterility, presence of HIV and hepatitis antigens, mutagenic effects); c) immunological properties (Migration Inhibition Factor production, Interferon, Interleukins 1 and 2, Tumour Necrosis Factor, IgG and IgM antibody production, rosettes forming tests, phagocytosis, influence on differentiation of bone marrow cells precursors, blast transformation activity, delayed type hypersensitivity). The obtained results may be considered as a proof of the immunostimulating properties of TF. That provides evidence for the use of TF in the treatment of ecological immunodeficiencies. Transfer Factor had positive effects in rehabilitation of immune system of irradiated mice. It was shown by normalization of the immunological parameters and increase of resistance to Staphylococcus aureus after TF administration to irradiated animals. We think that it may be due to direct influence of TF on differentiation of bone marrow cells precursors, T-mitogenic effects by means of stimulating cytokine production, and ability to modify T-cell receptor and activate membrane processes involving Ca2+ messengers.

Functional Activity Of Lymphocytes In Rats With Radiation Induced Hypothyreosis After Xenotransplantation Of Thyroid Gland Organ Culture And Immunostimulation With Transfer Factor

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The purpose of this investigation was to study the functional activity of lymphocytes from rats with radiation-induced hypothyreosis after xenotransplantation of newborn pig thyroid gland organ culture and the immunostimulating influence of transfer factor (purified and fractionated dialyzable leukocyte extract). Such transplantation didn't reduce immune activity of rat's splenocytes in vitro. Preparations of human and animal transfer factor activated thymidine incorporation into splenocyte's DNA, enhanced activity of macrophages and their antigen-presenting functions in intact animals as well as in rats with thyroid gland xenotransplant. There was also group of rats with irradiated thyroid gland, which function was substituted by injections. In this group we observed reducing of lymphocytes functional activity, which was successfully corrected by transfer factor. We concluded that xenotransplantation of thyroid gland organ culture didn't reduce immune activity of recipient's splenocytes and macrophages. Transfer factor can be used as a stimulator for immunodeficiency caused by thyroid gland dysfunctions.

Dialyzable Leukocyte Extract (Dle) Suppresses Transcription Factor Nf-Kb Activity In Unstimulated Mt-4 Cells

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Dialyzable Leukocyte Extract (DLE) derived from immune lymphocytes is capable of transferring specific immunity to naive T-cells. Clinical effectiveness of this biological extract has been demonstrated in a broad spectrum of diseases. Others have used DLE in AIDS patients and we observed a remarkable response in asymptomatic Human Immunodeficiency Virus (HIV)-infected individuals treated with DLE. Among the cellular transcription factors, NF-Kb plays a key role in the control of transcription of HIV, through the interaction with specific element from the long terminal repeat (LTR). In this work we examined the effect of DLE on NF-kB activation by EMSA, in cells that are commonly used to study HIV replication. The T-lymphocyte cell line MT-4 was exposed to several doses of DLE (0, 1.25 and 2.5 U/ml) during seven days, and nuclear extracts were prepared after 0, 3h, 3 and 7 days of treatment. Under these experimental conditions, we observed a remarkable inhibitory effect on NF-kB activity by DLE treatment. Reduction of DNA-protein complex formation was directly related with increments in DLE dose. Surprisingly, DLE at 2,5 U/ml completely suppressed NF-kB activation after seven days of MT-$ treatment. This effect is time related with the inhibition of HIV replication observed after DLE treatment in the same system, as we previously report. NF-kB is critical for proper immune function, cell growth and survival. Control of transcription by NF-kB represents a potential regulatory step of HIV gene expression. Our data indicate that DLE has the remarkable ability of inhibiting NF-kB DNA-binding activity. These results significantly contribute to our knowledge of the mechanisms responsible for the effectiveness of DLE therapy in asymptomatic HIV patients.

Inhibition Of TNF Alpha And TGF Beta1 In Mt-4 Cells Treated With Transfer Factor

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In 1954 Lawrence used the term Transfer Factor (TF) for a dialyzable extract of sensitized leukocytes, which transfers reactivity from skin test-positive donors to skin test-negative recipients. The immune system is regulated by a complex network of pleiotropic and redundant cytokines, which are continually secreted to a greater or lesser degree even then the system is apparently quiescent. Human Immunodeficiency Virus (HIV) directly infects cells of the immune system and triggers a robust immune response, which is an important and persistent source of immune activation. This activation is intimately linked to cytokine secretion. Numerous cytokines induce HIV expression, others suppress it, whereas others induce or suppress HIV expression, depending on the culture system used. Previously, our group reported that HIV production in MT-4 cells is inhibited after several days of treatment with TF. In this study, we evaluate gene expression of different cytokines on this cell line treated with TF. We showed that Transfer Factor inhibits the TNF alpha and TGF beta1 gene expression. IL-2 and IL-10 gene expression could not be observed in these culture conditions. It has been reported that TNFalpha induces HIV expression whereas TGFbeta1 increases or reduces it depending on the cell system used, Our results indicate that the inhibition of HIV production in MT4 cells by Transfer Factor could be in relation with the inhibition of the TNFalpha and TGFbeta1 gene expression by Transfer Factor in MT4 cells. These results may be relevant to the treatment of diseases where TNF and/or TGF plays a pathogenic role.

Decrease In Serum HIV RNA Following Treatment With A Leukocyte Dialysate Subfraction (Lds) That Contains N-Terminal Peptides Of The Enkephalins And Enhances Cell Mediated Immunity

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We have previously reported that a specific sub-fraction of human leukocyte dialysates affects cell-mediated immunity as demonstrated by augmentation and acceleration of delayed type hypersensitivity, enhancement of the expression of CD25 (the p55 component of the receptor for Interleukin-2) on CD4+ cells, and dose dependent biphasic enhancement of gamma-interferon production in response to mitogen. These effects appear to derive from the action of two peptides, Tyr-Gly and Tyr-Gly-Gly, which are structurally identical to the N-terminal end of the enkephalin neuropeptides.

Clinical testing of LDS in a double-blind randomized placebo controlled trial in HIV infected patients who were anergic and symptomatic, on entry, demonstrated a five-fold reduction in risk of progression to AIDS compared to placebo over six months of treatment. In patients with Rheumatoid Arthritis who had active disease and diminished proliferative responses to PHA, administration of LDS resulted in two-fold or greater augmentation of proliferative responses.

In a study of sera of a subset of patients with HIV disease from the above clinical trial matched on CD4+cell numbers at baseline (treated mean=299 cells/mm3, placebo mean =303 cells/mm3) we observed a 30% reduction in mean viral load over the course of the study in patients receiving LDS and a 239% increase in the mean number of viral copies in serum from patients who received placebo. Five of seven patients who received LDS showed a mean decrease in the HIV-RNA load of 50% (two patients showed a mean increase of 22%); five of the patients who received placebo showed a mean increase in HIV-RNA load of 370% (two showed a mean decrease in viral load of 89%). All LDS treated patients had a terminal decrease in viral load. LDS treated patients had a smaller decrease in CD4+ cell number than those who received placebo.

We believe these observations are supportive of the link between the neuroendocrine and immune systems and may help explain their role in modifying exacerbation and progression of the aforementioned disease states.

Transfer Factor's Role In Signal Transduction

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Transfer Factor (TF) is capable to transfer and induce antigen specific cell-mediated immune response. In our previous studies it was shown that human and animal TF preparations to Staphylococcus aureus antigen substances posses immunomodulating properties. The purpose of this investigation was to evaluate the mode of action on the membrane level. TF to St. Aureus corpuscular antigen influences on contraction of T.Coli guinea pig cell membrane with stable k+ polarization was investigated by means of a tensiometric method in an isometric system. It was found that TF had dose-response stimulating effects on contracting component of k+ membrane. The amplitude and the time of contraction increased by means of TF. It was concluded that TF has a modulating effect on Ca2+channels. It stimulates the Ca2+ transport into the cell. It is known that Ca2+ is one of the basic cell messengers that activates cell processes and can lead to cell differentiation and production of bioactive substances. It is one of the possible ways of activation of the immune response.

Peptide Sequences That Are Common To Transfer Factors

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The structures of molecules with transfer factor activity are unknown. Our attempts to sequence highly purified, intact transfer factor molecules were unsuccessful, presumably because the amino termini were blocked. Peptides prepared by glu-C digestion of purified transfer factors produced maps that suggested both highly conserved regions and variable regions that were similar to other antigen binding molecules.

Transfer factors that were specific for territin, ovalbumin or Herpes simplex glyco-protein D were prepared in mice and cattle and purified by affinityfor antigen and hplc. These molecules were digested overnight with cyanogen bromide and the cleavage fragments were sequenced. Two peptides. MxLLYAQDLEDN and MxLLYAQDVEDN were consistently obtained.

Synthetic peptides with the sequence LLYAQDLEDN did not sensitize mice to express delayed type hypersensitivity. Both peptides inhibited expression of delayed hypersensitivity by transfer factor-treated mice; LLYAQDLEDN was about 100x more potent than LLYAQDVEDN. Neither peptide inhibited expression of delayed type hypersensitivity in actively sensitized mice. The data are consistent with a model in which the peptides are competing with transfer factors for a common site (receptor?) on the target cells for transfer factors.

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