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ROLE OF GLUTATHIONE IN PHAGOCYTE HOST DEFENSE MECHANISMS

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The production of hydrogen peroxide in phagocytosing leukocytes is essential for the killing of microorganisms. Glutathione is thought to be involved in two ways in this process: 1) in the detoxification of the excess of H_2O_2; 2) as hydrogen donor in the production of H_2O_2. We were able to study the actual role of the glutathione redox system in the first known family with a real glutathione reductase deficiency in all blood cells.

We found that in contrast to normal cells, the oxygen consumption and H_2O_2 generation abruptly stopped 5-10 minutes after the onset of phagocytosis. This effect was probably due to cell injury since the patients' granulocytes and monocytes, after pre-incubation with an H_2O_2-generating system, did not react any longer with phagocytosable particles. The generation of superoxide radicals (O_2^-), intermediates in the formation of H_2O_2, was normal in the patients' granulocytes, indicating that glutathione is not involved in the production of these compounds. Most likely, the cytochrome c, used for the detection of O_2^-, prevented efficient generation of H_2O_2, thus protecting the cells against its harmful effects. The lack of recurrent infections in these patients and the normal in vitro phagocytosis and killing of Staphylococcus aureus indicate that the short respiratory burst suffices for effective host defense. Moreover, the occurrence of hemolytic crises after eating of fava beans and the development of cataracts in this family indicate that glutathione fulfils an essential role in the protection of many different cells against oxidative stress.

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PURE MONOCYTIC LEUKEMIA IN A 9 YEAR OLD BOY.

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Acute leukemia was diagnosed in apreviously healthy boy, during a febrite respiratory infection. The clinical findings were fever and residua of a pneumonia. The liver was slightly enlarged. Skin and mucous membranes were unaffected and there was no lymphadenopathy.

The leucocyte count was 49.7 x 10^9/l, with 68% blasts. The same blast cells infiltrated the bone marrow almost completely. The MGG-stained blasts resembled mature monocytes, with slightly basophilic cytoplasm. The nuclei were mostly lobulated or irregular, and contained 0-2 nucleoli. Some binucleated cells were seen. The cells were not stained with Sudan B, but they contained fine PAS-positive granules and were strongly positive for α-naphtyl acetate esterase. Auer rods were not seen and the few myeloid cells in the peripheral blood were strongly alkaline phosphatase positive. The lysozyme concentration in urine was enormously elevated to 800-1.000 µg/ml.

The leucemic cells did not form rosettes with sheep RBC and were negative for surface bound IgG. About 70% of the blasts formed rosettes with IgG coated human RBC, which indicates a high density of membrane Fc-receptors.

The karyotype of bone marrow cells was 44, X, -15, -21, +mar, del (2) (p11). The missing Y chromosome could be demonstrated in the marker chromosome. The karyotype of peripheral blood lymphocytes was normal, 46, XY. The morphology of the cells, the histochemistry and membrane Fc-receptors all indicate that the blasts belong to the monocytic series. Pure monocytic leukemia in childhood is extremely rare and detailed case reports including chromosomal abnormalities are scarce.

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L-ASPARAGINASE AS A THIRD DRUG FOR REMISSION INDUCTION IN ALL. EFFECT ON REMISSION DURATION IN A RANDOMIZED PILOT STUDY

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Recent evidence suggests that the effect of the addition or omission of a drug to or from a treatment protocol for ALL depends on the context of the whole program (1). A pilot study was undertaken to test the effect of L-asparaginase on remission duration in children with ALL under treatment protocol "Freiburg 71", which is similar to Memphis protocol "Total VII"(2).

30 children with ALL were randomized to receive either vincristine+prednisone or vincristine+prednisone+L-asp (1000E per kg once weekly x5, each dose being applied 24 h after VCR). Induction in both groups was followed by cranial irradiation (2400 rad) and i.th. MTX. Remission was maintained by oral 6-MP (50 mg/m²/d) + alternating 8-week courses of MTX (75-150 mg/m²/2wk. i.v. x4) and cyclophosphamide 600 mg/m²/2wk. i.v. x4).

13/15 children achieved remission in each group. Considerable toxicity of L-asp was observed from the third L-asp infusion on. After an observation time of 24-56 (median 42) months 8/13 children are in continuous remission in the VCR+pred+L-asp-group compared to 5/13 children in the VCR+pred-group.

L-asp improves the results of this treatment protocol.

Ref.: 1)Simone, J.V.: Brit. J. Haematol. 32, 465 (1976)
2)Wehinger, H. et al.: Strahlentherapie 148, 590 (1974)

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SERUM THYMIC FACTOR (SF) IN SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE) PATIENTS

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SSPE, a disorder of the central nervous system associated with a persistent measles infection, has been suggested to be related with immunodeficiency of the thymus dependent system.

We investigated the level of SF, as reported (1), in 9 children with SSPE. In addition we tested patients lymphocytes for: a) the effect of SF from normals on intracellular levels of cAMP; b) PHA, Con A, PWM, MLC and antigen responsiveness "in vitro"; c) E-rosette formation.

We found that patients could be divided in 2 groups: 6 with very low and 3 with normal SF activity. SF from normals had virtually no effect on cAMP levels in lymphocytes of 5/6 patients of the first group, but strongly increased cAMP in 3/3 of the second group. No clear abnormality was found among the other examined parameters. One patient(with very low SF activity and with lymphocytes that could be stimulated to increase cAMP by SF from normals) was treated with the thymic hormone preparation "thymosin". Shortly after treatment was started, SF-like material was demonstrable in the serum of the patient. This correlated with some immunological changes but not with clinical changes.

Our findings indicate that the humoral function of the thymus might be altered in some SSPE patients. It remains unclear if this is a result or rather one of the causes of the disease and whether thymic hormone treatment might be of benefit in some SSPE patients.

1) Astaldi, A et al., Nature 260, 713-715 (1976).

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MEMBRANE MARKERS IN ALL : A STUDY OF 21 CASES

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Twenty one cases of ALL (13 males,8 females) were analysed for the presence of T and B membrane markers in blood or bone marrow prior to treatment.Their ages were between 2 and 16 years. E rosettes with SRBCs (at 4° and 37° C) and with autologous RBCs, HEA and HEAC rosettes were performed.The surface immunoglobulins(with monospecific antisera to µ,γ and κ chains) were detected by using a direct immunofluorescence technique. Seven(33%) were T cell;1 (4%) was B cell; and 13(62%) were considered to be null cell type.The male:female ratio was 5:8 in null cell; 7:0 in T cell type.Two cases of T cell type had mediastinal lymphadenopathy.There was no significant difference for the WBC counts between the T and null cell groups.During the first 6 weeks of treatment,50% of the patients with T cell type and 10% of the patients with null cell type did not go into remission with classical induction therapy.Forty-two percent of the patients with T cell type and 7% of the patients with null cell type had CNS infiltration.Forty-two percent of the patients with T cell type and 12% of the patients with null cell type died during the observation period of this study.

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PRELEUKEMIA IN FANCONI'S ANEMIA - CLONAL EVOLUTION

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Chromosome follow-up studies were performed over a 10-year period in a 17-year-old male with Fanconi's anemia. At the age of 14, following androgen therapy, the patient had experienced a hematological remission which was maintained for the next 3 years with no further therapy. The typical chromosomal aberrations found in the peripheral blood lymphocytes of patients with Fanconi's anemia decreased from 78% at the time of diagnosis to 42% at puberty. At the age of 16, while the patient was in complete remission, an abnormal clone with an elongated long arm of Group A chromosome evolved in the patient's bone marrow. This clone, which gradually gained dominance in the marrow, penetrated to the peripheral blood 6 months later. Using banding techniques it was possible to identify and clarify the mechanism of its evolution, i.e. its origination from a broken, rearranged chromosome, which provides supportive evidence for a defective DNA repair in Fanconi's anemia.