17 PROFOUND TOXICITY OF DEOXYADENOSINE (dAdo) AND 2-CHLORODEOXYADENOSINE (CdA) TOWARD HUMAN MONOCYTES *IN VITRO* AND *IN VIVO*. Carlos J. Carrera, Hisashi Yamanaka, Lawrence D. Piro, and Dennis A. Carson. Research Institute of Scripps Clinic, La Jolla, CA USA.

dAdo is known to be toxic to both proliferating and resting lymphocytes that lack adenosine deaminase (ADA) activity. We now show that human monocytes are also highly sensitive *in vitro* to nM concentrations of dAdo plus the ADA inhibitor deoxycoformycin, and to the ADA-resistant analog CdA. The dose- and time-dependent toxicity of dAdo or CdA to monocytes is blocked by deoxycytidine, implicating deoxycytidine kinase in the formation of toxic dAdo or CdA nucleotides. Monocytes exposed to dAdo plus deoxycoformycin, or to CdA accumulate massive DNA damage detectable within 1 hour. The accumulation of DNA strand breaks in lymphocytes stimulates the lethal consumption of NAD and ATP for poly(ADP-ribose) synthesis. However, monocytes lack the poly(ADP-ribose) polymerase enzyme and therefore show no significant NAD or ATP depletion until cell viability declines (12 hr). The DNA damage in monocytes exposed to CdA is associated with a decrease in protein synthesis *in vitro*, and with inhibition of IL-6 secretion. The selective toxicity of CdA to monocytes was confirmed by *in vivo* studies. Thus, the blood monocyte counts, but not the neutrophil counts, fell to 0 in one week in nearly all patients receiving CdA infusion chemotherapy for cutaneous lymphoma. These results show that dAdo and CdA cause DNA strand break formation and inhibit protein synthesis in human monocytes *in vitro*, and cause profound monocytopenia *in vivo*. These compounds may have potential use in the therapy of immune disorders associated with monocyte/macrophage activation.

18 POTENT ACTIVITY OF 2-CHLORODEOXYADENOSINE IN CHRONIC LYMPHOCYTIC LEUKEMIA, HAIRY CELL LEUKEMIA, AND AUTOIMMUNE HEMOLYTIC ANEMIA. Dennis A. Carson, Lawrence D. Piro, D. Bruce Wasson, Carlos J. Carrera, and Ernest Beutler. Research Institute of Scripps Clinic, La Jolla, CA USA.

Unlike other nucleoside anti-metabolites, 2-chlorodeoxyadenosine is selectively toxic at nanomolar concentrations to human lymphocytes and monocytes. In susceptible cells, the drug causes a dose- and time-dependent accumulation of DNA strand breaks, with resultant activation of poly(ADP-ribose) polymerase. Furthermore, the actions of 2-chlorodeoxyadenosine are entirely independent of replicative DNA synthesis. For this reason, we reasoned that 2-chlorodeoxyadenosine would represent a useful agent for the treatment of slowly replicating lymphoid malignancies, and for the therapy of chronic autoimmune diseases. In the present study, 2-chlorodeoxyadenosine was administered to 18 patients with advanced chronic lymphocytic leukemia, 4 of whom had concurrent autoimmune hemolytic anemia. An overall response rate of 56% was achieved. Only minor and reversible bone marrow suppression occurred during treatment, indicating a high degree of lymphocyte selectivity. Moreover, 3 of the 4 patients with autoimmune hemolytic anemia had complete resolution of hemolysis. Three patients with hairy cell leukemia also received 2-chlorodeoxyadenosine therapy. Two of the patients achieved clinical remission after one course of the drug. These results demonstrate that 2-chlorodeoxyadenosine is a safe and potent anti-lymphocyte and immunosuppressive agent. Further trials of the drug in autoimmune and lymphoproliferative diseases are warranted.

19 2-HALO-2',3'-DIDEOXYADENOSINES: METABOLICALLY STABLE DIDEOXYNUCLEOSIDES WITH ACTIVITY AGAINST THE HUMAN IMMUNODEFICIENCY VIRUS (HIV). Dennis A. Carson, Thomas Haertle, Carlos J. Carrera, Erik H. Willis, D. Bruce Wasson, and Douglas D. Richman. Research Institute of Scripps Clinic, Department of Basic and Clinical Research, La Jolla, CA, USA, and University of California, San Diego/Veterans Administration Medical Center, San Diego, CA, USA.

2',3'-dideoxyadenosine (ddA) has activity against the human immunodeficiency virus-1 (HIV), but is rapidly catabolized by human T cells, even when adenosine deaminase is inhibited by deoxycoformycin. To overcome this problem, we developed a simple method to synthesize the 2-fluoro-, 2-chloro-, and 2-bromo-derivatives of ddA. The isolated 2-halo-ddA derivatives were not deaminated significantly by cultured T lymphoblasts, which converted the dideoxynucleosides to the respective 5'-monophosphate, 5'-diphosphate, and 5'-triphosphate metabolites. At concentrations lower than those producing cytotoxicity in uninfected cells (3-10 μM), the 2-halo-ddA derivatives inhibited the cytopathic effects of HIV toward T lymphoblasts, and retarded viral replication. Experiments with a deoxycytidine kinase deficient mutant CEM T cell line showed that this enzyme was necessary for the phosphorylation and anti-HIV activity of the 2-halo-ddA derivatives. Thus, the 2-halo-ddA congeners, in contrast to ddA itself, are not degraded by T lymphocytes, and represent promising compounds for *in vivo* chemotherapy of HIV infection.

20 CLINICAL ASPECTS OF GOUTY PATIENTS IN TAIWAN Ching-Lang Chen, Naoyuki Kamatani, Kusuki Nishioka and Kiyonobu Mikanagi, Clinic of Gout, Taipei Municipal Ho-Ping Hospital, Taipei, Taiwan, R.O.C. and Institute of Rheumatology, Tokyo Women's Medical College, Tokyo, Japan

Before World War II, the incidence of gout had been low in Taiwan and has begun to increase only after the war, probably reflecting the change of the diet due to the economical development and improved standards of living in the country. Since our clinic was established in 1983, we have seen a total number of approximately 4,000 patients with gout. The diagnosis of gout was made according to the criteria proposed by the American Rheumatism Association. For every gouty patient visiting our clinic for the first time, the serum urate concentration and the amount of urate in the 24-hour urine were examined. The serum urate concentration was checked at 2 months intervals in order to monitor the effects of drugs. In addition to these tests, general data including hematological findings, serum biochemistry information, urine analysis, renal function, chest X-ray examincation and EKG were obtained every one year for each patient. The data from these 4,000 patients have been accumulated and submitted to the analysis by a computer. Based on such clinical and laboratory observations and the results obtained by the analysis, we discuss about characteristic features of gout in people in Taiwan.

21 DETECTION OF LOW ECTO-5'NUCLEOTIDASE ACTIVITY IN MONONUCLEAR CELLS FROM PATIENTS WITH DEFECT T LYMPHOCYTE FUNCTION. Lisa D. Christensen[1], Per Nygaard[3], Johannes Mejer[2] and Viggo Faber[1]. Dept. of Infectious Deseases, University Hospital, Blood serology Dept., Bispebjerg Hospital Copenhagen, Denmark.

A retrospective study of 49 patients with/or suspected for an immune disease was done to enable a comparision between levels of purine en-zymes in mononuclear cells and some frequently used markers of immune function. A new observation was the finding of correlation between low ecto-5'nucleotidase activity and decreased T lymphocyte function measured as decreased lymphocyte proliferation after mito- and antigenic stimulation in vitro. In this study we did not find correlation between the activity of ecto-5'nucleotidase and the other investigated markers of immune function (lympfocyte count, lymphocyte subpopulations, concentration of immunoglobulines in serum and lymphocyte proliferation after mito- and antigenic stimulation in vitro). The activities of adenosine deaminase and purine nucleoside phosphherylase in mononuclear cells were also measured. In this group of patients no correlation was find between the activities of these enzymes and the investigated markers of immune function.

22 THE ACTIVITY OF ECTO-5'NUCLEOTIDASE IN CULTURED MONONUCLEAR CELLS IS REGULATED BY INTERACTIONS BETWEEN MONOCYTES AND LYMPHOCYTES Lisa D. Christensen[1], Morten Svenson[1], Vagn Andersen[2] and Viggo Faber[1]. Dept. of Infectious Diseases and Dept. of Medicine TTA, University Hospital, Copenhagen, Denmark.

The activity of ecto-5'nucleotidase on mononuclear cells isolated from freshly drawn venous blood change during culture. The measured ecto-5'nucleotidase activity on mononuclear cells was much higher than the activity estimated from lymphocytes and monocytes when cultivated separately. The average ecto-5' nucleotidase activity on mononuclear cells after 2 days culture was 86.8 nmole product developed/h/10^6 cells (U/10^6 cells) whereas the activity before culture was 22.0 U/10^6 cells. After the same period in culture the activity in lymphocytes and monocytes cultivated separately was 21.2 U/10^6 cells and 126.2 respectively.

These results indicate that the activity of ecto-5'nucleotidase on cultured mononuclear cells is regulated by interactions between lymphocytes and monocytes.