toxicity was found for the compound in these tests. The ability of this and other compounds in the series to act as thymomimetic agents in inducing a surface antigen (Thy-1.2) in lymphocytes from nude, athymic mice has been compared with levamisole, D-penicillamine and serum thymic factor. Like levamisole, but not D-penicillamine, several of the compounds are potent thymomimetics. Evidence has been obtained that a structurally related compound acted as an antagonist of the former compound, both in vivo and in vitro. In view of the therapeutic potential of thymic hormones in the modulation of immune responsiveness, a role is indicated for such thymomimetic compounds in diseases with an underlying immunological defect.

46 REGIONAL IMMUNOTHERAPY OF GUINEA PIG LINE-10 HEPATOMA WITH CHEMICAL HYPERSENSITIZERS

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Regional immunotherapy in which agents are administered to localise within tumour deposits and promote local host responses, including hypersensitivity reactions, is being widely evaluated for cancer therapy. Originally intact bacteria, principally BCG and C. parvum, were used, but these have toxic side effects, and attention is now directed to developing more defined agents.

The present studies are evaluating regional immunotherapy with alkylcatechols related to the natural plant oil urushiol. These were chosen since they are highly potent hypersensitising agents with marked lipophilicity (Byers et al. J. Clin. Invest., 64, 1437, 1979). With intact viable rat and guinea pig hepatoma cells, ^{3}H-3-n-pentadecylcatechol (PDC) became incorporated into cell membranes on in vitro incubation. Intradermal growth of the guinea pig line-10 hepatoma was restricted by intralesional injection of PDC or urushiol, and there was a concomitant control of lymph node metastases. Although effective in DMSO solution, the response was considerably enhanced when PDC was given in a lipid solvent (squalene). Pre-induction of contact sensitivity to PDC also enhanced the therapeutic response.

These studies demonstrate that chemically defined agents, inducing T-lymphocyte mediated delayed hypersensitivity responses, can be used for regional tumour immunotherapy

47 ON THE IMMUNOMODULATORY ACTIVITY OF NPT 15392: IN VITRO EFFECTS ON MOUSE AND HUMAN CELLS

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Initial studies aimed at characterizing the immunomodulatory activity of NPT 15392, a novel heterocyclic drug, have been conducted in vitro on human and murine lymphoid cells. The exposure of peripheral blood lymphocytes (PBL) from normal individuals to 10^{-4} - 10^{-1} ug/ml NPT 15392 concomitant with mitogen has produced significant increases in ^{3}H-TdR uptake; the increase was most pronounced (e.g. 70-100% increase in S.I. after PHA) at suboptimal mitogen concentration. An increase in mitogen response was also observed with PBL from some cancer patients; similarly, in a proportion of ovarian cancer subjects, lymphocytes isolated from the tumorous ascites showed enhanced mitogen reactivity after treatment with the compound. Conversely, non specific cytotoxicity of peripheral blood monocytes from normal donors and of peritoneal macrophages from normal subjects and ovarian cancer patients against mKSA-TU5 tumor target cells was unaffected by in vitro NPT addition.
In mice, splenocyte stimulation by PHA and LPS was increased by NPT in vitro at concentrations of 10^{-2} -10^{0} ug/ml whereas no modification was found in peritoneal macrophage non specific cytotoxicity against mKSA-TU5 target cells. Moreover, in vivo parenteral administration of NPT (10 mg/kg) for 4 days to normal mice starting on the day of antigenic stimulation significantly increased the primary antibody response.
These data suggest that NPT in vitro affects directly lymphocytes but not cell of monocyte-macrophage line: in addition these findings show that the compound is able to modify the immune reactivity of lymphocyte with normal capability to respond to antigenic challenge.

CP-46,665, A NOVEL ANTIMETASTATIC AGENT 48

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CP-46,665, 4-aminomethyl-1-(2,3-(di-n-decyloxy)-n-propyl)-4-phenylpiperidine dihydrochloride, is a novel, low molecular weight, synthetic compound with anti-metastatic activity in rodent models. In the B16 melanoma/C57b16 mouse system, in which the hind limb bearing a primary foot tumor is amputated 21 days after tumor implantation, experience with 322 animals in 35 experiments shows that 19% of the animals will be free of melanotic lung metastases on day 50. Intravenous infusion of CP-46,665 after surgery, at doses ranging from 0.15 to 10 mg/kg, increases the fraction of metastases-free animals to as high as 56% (significantly different from surgery-only controls at $p < 0.001$). In more preliminary experiments in a mammary adenocarcinoma (13762)/Fischer 344 rat system, there are suggestions that combination of CP-46,665 infusion with surgical removal of the primary tumor also results in increased numbers of long-term survivors that are free of metastatic disease. Investigation of effects in a variety of other tumor models are in progress.

The mechanisms underlying the anti-metastatic activity of CP-46,665 are not clear, but certain lines of evidence suggest that the compound may act via effects in the lymphoreticular system. Peritoneal macrophages from animals dosed with CP-46,665 display elevated cytolytic activity against tumor target cells. Further, radio-labeled CP-46,665 and/or its metabolites preferentially accumulate in organs of the lymphoreticular system, and we have noted that lymph nodes, spleens, and livers from animals dosed chronically with CP-46,665 contain scattered foci of histiocytic cells or Kupfer cells (liver) with foamy vacuoles containing material staining as lipid. Interferon is not induced in rodents by CP-46,665, and the agent does not provoke or augment mitosis in spleen or thymus cells. Direct cytotoxic effects on tumor cells are present at an IC_{50} of $\sim 5 \times 10^{-5}$M.

CP-46,665 appeared reasonably well-tolerated in rats and dogs infused at doses of up to 25 mg/kg at 4 day intervals for 92 days. In addition to the changes in the lymphoreticular system described above, principal findings in the high-dose dogs were erythrocyte lysis accompanied by the expected serum chemistry and hematological correlates. In the high dose reats, microcytic anemia and injection site irritation were the most significant findings. Neither species displayed notable toxic reactions when chronically dosed at the 1 mg/kg level, a level well within the antimetastatic activity dose range. Cats and dogs with a variety of malignancies tolerated weekly doses of the agent as high as 5 mg/kg with minimal side-effects for periods up to 30 weeks. We feel that this combination of good chronic toleration and potent antimetastatic activity commend CP-46,665 well for more extensive study as an experimental drug for the treatment of cancer.

LYNESTRENOL, A PROGESTERON-LIKE AGENT WITH IMMUNOMODULATORY PROPERTIES IN MAN : IN VITRO AND IN VIVO (CANCER) RESULTS 49

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Lynestrenol, a synthetic progesteron-like drug, has been tested for its immunologic properties. Lynestrenol was found to markedly enhance blood human lymphocyte response to phytohemagglutinin and in mixed lymphocyte culture. It also increased the percentages of active T rosettes. It enhanced the phagocytosis of yeast particles by human monocytes. None of these properties were sex related. When given to cancer patients, lynestrenol also stimulated their T cell functions as judged by the induction of skin reactivity to antigens, the augmentation of blood lymphocyte PHA response and the increase of blood active T rosettes. Serum autoantibodies levels were also modified during the treatment. Finally, lynestrenol delayed, in hamsters, the appearance of malignant tumor growth and increased survival. All these observations indicate T cell immunomodulatory properties of lynestrenol.

CELL MOVEMENT

PHARMACOLOGIC MODULATION OF POLYMORPHONUCLEAR LEUKOCYTE (PMN) LOCOMOTION: EFFECT ON RATES OF RADIAL MIGRATION UNDER AGAROSE 51

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Locomotion of PMNs is an integrative process requiring coordination of membrane and intracellular functions. When experimental conditions permit measurement of translational movement of PMNs, rates of chemically-stimulated movement parallel other parameters of PMN activation, such as oxygen consumption, chemiluminescence, phagocytosis and lysosomal degranulation. Therefore alteration of *rates* of movement could be a sensitive indicator for pharmacological modulation at several levels of PMN function.