ANGIOGENESIS-DEPENDENT PROCESSES UNDER EXPOSURE TO HYPOXIA AND PERSPECTIVES FOR THE DEVELOPMENT OF HYPOXIC THERAPY

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INTRODUCTION. A variety of physiological and pathological angiogenesis-dependent processes are suppressed by hypoxic environment such as high altitude. Wound healing is delayed. Ovarian and endometrial functions are inhibited under high altitude hypoxia. Birth weights decline with altitude. A strong inverse correlation was found for geographical altitude and the incidence of bronchial asthma. The incidence of psoriasis and eczema is lower in mountain regions. A negative association was found between atherosclerosis and altitude of residence. Cancer incidence and cancer death rates are reduced at high altitude. Leukemia mortality rate is lower in mountain residents than in plainsmen.

METHODS. Hypoxic therapy is based on breathing air with partially reduced oxygen pressure. The different techniques of hypoxic therapy include: mountain (climatic), hypobaric, and normobaric hypoxia. It has been demonstrated in more than 500,000 patients that intermittent breathing a hypoxic gaseous mixture containing 10% O2 and 90% nitrogen (HGM-10) is a safe and effective method of hypoxic therapy (1).

RESULTS. A accumulating evidence indicates the beneficial effects of hypoxic therapy on clinical course of different chronic diseases. Clinical observation for thirty years experience showed that inter mitten hypoxic therapy with HGM-10 exerted a pronounced therapeutical effect in patients with atherosclerosis, chronic obstructive bronchitis, bronchial asthma, chronic nonspecific salpingoophoritis, and periodontal disease. Antipsoriatic treatment is more effective in combination with hypoxic therapy. Hypoxic training is also used in obesity. In clinical oncology adaptation to hypoxia is used for restoration of hemopoiesis after radiation and chemotherapy. Furthermore, experimental data have shown that host exposure to hypoxia suppresses tumor development. The experiments on 2,700 tumor-bearing animals have demonstrated that in the Tien-Shan mountains, at an
altitude 3,200m above sea level, the growth transplantable tumors is 36-69% inhibited as compared to the control at low altitude (760m). The mean survival time of tumor-bearing animals at high altitude was increased by 20-40% as compared with low altitude. Along with the inhibiting effect on the growth of the primary tumor, altitude hypoxia suppresses metastatic spreading. It was shown under alpine conditions in mice with Lewes lung carcinoma a 1.8- fold decrease in number of lung metastases. In mice with Ehrlich adenocarcinoma the frequency of metastatic spreading into regional lymph nodes was 2-fold decreased. Exposure to hypoxia in hypobaric chamber at the altitude 5,000m for 6 hours daily during 3 weeks also inhibited the growth of transplantable tumors.

DISCUSSION. Mammals responds to reduced oxygen concentration in many different ways: at cellular, local, and organism levels. Central and peripheral nervous systems control organism response. The cellular response is mediated by hypoxia-inducible factors (HIFs). Exposure to hypoxia in vivo induces in each organ different HIF-1 expression kinetics (2). Under hypoxic conditions blood flow is redistributed with centralization to vital organs by vasodilation, increasing vascular permeability and angiogenesis. It is appears that exposure to hypoxia modulates host response to tumor signaling because angiogenic stimulators such as VEGF are induced in normal tissues. It seems it is possible to reduce the blood volume within the tumor by shunting blood flow from the tumor to normal tissues. A multitude of VEGF-targeted agents are currently being investigated for the treatment of cancer (3). These agents may affect VEGF functioning in normal tissues and damage vascular defense of the host. An attractive possibility is that hypoxic training of the host may be used to decrease toxicity and increase efficacy of targeted antiangiogenic drugs.

REFERENCES.