EXPERIMENTAL INFLAMMATION AND TUMOR GROWTH
Chemical Carcinogenesis in Adjuvant Arthritic Rats

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Abstract—Development and growth of primary (methylcholantrene or benz-pyrene-induced) sarcomas in adjuvant arthritic rats were investigated and compared with the chemical carcinogenesis in normal healthy animals. When carcinogen and adjuvant were applied in the same time, tumor development and growth rate did not differ significantly from nonarthritic controls. When carcinogen was applied to rats with fully established arthritic disease, development and growth of tumors were significantly enhanced. In the latter case local and systemic adjuvant disease was more severe in tumor-bearing rats. Enhanced chemical carcinogenesis in arthritic rats can be explained by a defective immune responsiveness in the chronic stage of arthritis.

INTRODUCTION

There are two quite opposite hypotheses for the relation between rheumatoid arthritis and cancer. There is a general awareness that rheumatoid arthritis can be the initial manifestation of malignancy (1), while an unexpected low frequency of neoplasm in rheumatoid arthritic patients borne out by the statistics (2) raised the question of protection.

The nature of the link between the two diseases is important from another practical point. The increased incidence of cancer in patients with immunodeficiencies or in those undergoing immunosuppressive therapy supplied evidences that depressed host defense system has an important role in development of neoplasms. On the other hand the state of immune function in rheumatoid arthritis is a question open for debate. The basic question of immunotherapy of rheumatoid arthritis is: immunosuppression or immunostimulation? There is no strong evidence for and against both of the two therapeutic alternatives (3). Although experiments have shown a
depression of the inflammatory response in animals bearing neoplasms (4–8) no information is at present available about incidence and growth of neoplasms in chronic arthritic disease such as adjuvant arthritis in the rat.

The aim of the present work was to study the interaction between polyarthritic syndrome and tumor growth under experimental conditions.

MATERIALS AND METHODS

Animals. Male Sprague-Dawley (CFY) rats, weighing 150–160 g, were used throughout the experiments. They were obtained from the Animal Breeding Centre (LATI) at Budapest and were maintained in our laboratory on standard diet and drinking water ad libitum.

Sarcoma Induction. 3-Methylcholanthrene (Sigma) or 3,4-benz[a]pyrene (Fluka) dissolved in helianthy oil was injected subcutaneously at dose of 15 mg into the subscapular region of rats. These carcinogens in the applied dose induced 100% tumors under our conditions. Tumor development was monitored by weekly palpation of the animals. The size (diameter) of the tumors was determined by caliper measurement of two diameters and tumors were allowed to develop until they reached a mean diameter of 2 cm. The time after carcinogen until tumors became palpable and achieved the size given above were determined.

Adjuvant Arthritis. Complete Freund's adjuvant (heat killed Mycobacterium tuberculosis) was suspended in paraffin oil (0.6 mg/0.1 ml) and injected into the left hindpaw of the rat. Severity of arthritis was evaluated visually (0–4 score for each paw, maximum 16 score per animal), and the paw volumes were recorded by mercury displacement. Controls were treated subcutaneously with the same volume of oil without carcinogen and they received 0.1 ml incomplete adjuvant (liquid paraffin only) into their paws.

RESULTS

Development of primary sarcomas in rats injected subcutaneously with carcinogen at the time when adjuvant was administered into their paws are shown in the first part of Figures 1 and 2. Compared to nonarthritic controls, sarcomas induced by chemical carcinogens became detectable in arthritic rats slightly (not significantly) later, but after being palpable, they grew further at the same rate. As to the intensity of joint alterations, there were no significant differences in the incidence and severity of arthritic reactions between arthritic and tumor-bearing arthritic rats (Table 1).

In the second part of our experiments, chemical carcinogens were administered to rats with severe established generalized adjuvant arthritis. Large numbers of rats were treated with adjuvant, and 28 days thereafter rats with intense generalized arthritic reactions (score per animal >12) were selected and treated subcutaneously with carcinogens. As is shown in the second parts of Figures 1 and 2, the time of the appearance of tumors was significantly shortened in rats being severely arthritic at the time of carcino-