EFFECT OF CHANGES IN REACTIVITY PRODUCED BY FREUND'S COMPLETE ADJUVANT ON THE DEVELOPMENT OF INDUCED TUMORS IN RATS

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Freund's complete adjuvant, if injected into rats before or after administration of methylcholanthrene, increases the incidence of tumor development in the animals. This effect is particularly marked if the adjuvant is injected before administration of the carcinogen.

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Freund's complete adjuvant is a factor with powerful immunologic action: it considerably increases antibody production in response to injected antigens, and promotes the development of autoimmune and autoallergic processes in the body. Recently cases of the use of adjuvants of this type in clinical practice have been described, especially in the treatment of malignant neoplasms [4, 6, 7].

This use of adjuvants of the Freund type in clinical practice and on a wide scale in experimental oncology has raised the question of how these substances by themselves, without any additional immunologic procedure, affect tumor development. Investigations along these lines are also of theoretical interest, for they help to elucidate the role of autoimmune and autoallergic changes in reactivity of the body in general changes in its resistance to the development and growth of tumors.

The object of this investigation was to determine how Freund's complete adjuvant affects the resistance of the body to the action of a chemical carcinogen.

EXPERIMENTAL METHOD

Experiments were carried out on 59 female Wistar rats aged 8 months. There were two series of experiments: in series I 12 rats received Freund's complete adjuvant 10 days before administration of the carcinogen and 17 rats received the adjuvant 10 days after administration of the carcinogen; 12 animals (control) received the carcinogen only.

The experiments of series II differed from the first series in being conducted on animals vaccinated with BCG. The rats were vaccinated by intraperitoneal injection of 5 mg of living vaccine 3.5 months before administration of the carcinogen. Of the 18 animals in this series, half received Freund's complete adjuvant before injection of the carcinogen and half after its injection. In the experiments of series II the adjuvant was injected at the same times as in series I. The idea behind the experiments on vaccinated animals was to determine how specific sensitization to Freund's complete adjuvant is reflected in the resistance of the body to tumor development. Freund's complete adjuvant was made up in the proportion of 10 mg killed tubercle bacilli to 1 ml 50% water-oil emulsion (mineral oil was used). A single injection of 0.03 ml of the emulsion was given subcutaneously into the left hind limb. Methylcholanthrene, dissolved in apricot oil (10 mg/ml), was used as the carcinogen and was injected subcutaneously into the left thigh in a dose of 1.5 mg/100 g body weight. The results were subjected to statistical analysis.

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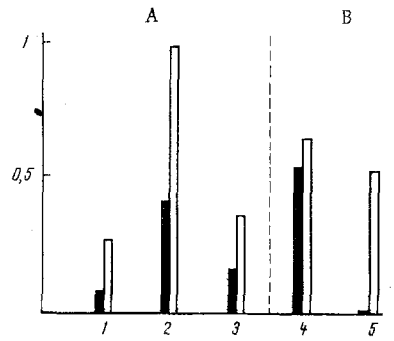

Fig. 1. Effect of Freund's complete adjuvant on development of tumors in rats: A) experiments of series I; B) experiments of series II. Ordinate, proportion of total number of rats developing tumors; 1) control; 2 and 4) adjuvant injected 10 days before administration of carcinogen; 3 and 5) adjuvant injected 10 days after administration of carcinogen. Black columns show number of tumors after 4 months; unshaded columns number after 5 months.

EXPERIMENTAL RESULTS

On the 13th day after injection of Freund's complete adjuvant 13 of the 29 unvaccinated and 8 of the 18 vaccinated animals developed polyarthritis, i.e., the relative proportion of cases was about the same.

It is clear from Fig. 1 that Freund's complete adjuvant facilitated tumor development, especially if given 10 days before injection of the carcinogen.

For instance, of the 12 rats in series I which received Freund's complete adjuvant at these times, 5 developed tumors after 4 months, and all 12 animals did so after 5 months. In series II, of 9 vaccinated rats subjected to the same treatment, 5 developed tumors after 4 months and 6 animals did so after 5 months. By contrast, in the control group of animals the number of tumors appearing after these times was much smaller; after 4 months only 1 of the 12 rats, and after 5 months 3 of the 12 rats, had developed a tumor.

The difference between the numbers of animals with tumors in the group of rats receiving Freund's complete adjuvant 10 days before administration of the carcinogen and the numbers of control animals developing tumors are statistically significant: for unvaccinated animals after 4 and 5 months, respectively, $0.05 > P < 0.01$, and for vaccinated animals $0.02 > P < 0.05$.

In the case when Freund's complete adjuvant was given 10 days after injection of the carcinogen, an increase in the number of tumors arising was observed both in the intact rats (after 4 and 5 months tumors appeared in 3 and 5 of the 17 animals, respectively), and in the vaccinated animals (after 4 months no animal had developed a tumor, but after 5 months tumors were found in 5 of the 10 animals). However, differences from the control were not statistically significant: for these same times, in the intact animals $0.2 < P > 0.5$, and in the vaccinated animals $0.5 < P > 0.1$.

In the experiments of series I and II, the latent period of tumor development was shorter in animals receiving Freund's complete adjuvant before injection of the carcinogen (138 and 138 days, respectively) than in animals receiving the adjuvant after the carcinogen (153 and 149 days), and the difference was particularly marked when compared with the control animals (161 days).

Freund's complete adjuvant, if injected into the plantar pad, produces sharp changes of reactivity which lead to the development of polyarthritis on about the 13th day [1-3]. Some workers consider that this polyarthritis is due to the onset of autoimmune processes in the body [5].

In these experiments the highest incidence of tumors occurred among those animals receiving the carcinogen at times close to the appearance of this polyarthritis (i.e., 10 days after administration of Freund's complete adjuvant). In the writer's opinion, this fact is evidence to support the view that the lowering of resistance to tumor development observed in these experiments is due to changes in reactivity facilitating the development of autoimmune processes in the body.

LITERATURE CITED

1. Y. Akamatsu et al., Acta Path. Jap., 16, 131 (1966).
2. E. M. Glenn, Am. J. Vet. Res., 26, 1195 (1965).
3. C. M. Pearson and F. D. Wood, J. Exp. Med., 120, 547 (1964).
4. E. Robinson and E. Ratzowski, Gynaecologia (Basel), 160, 87 (1965).
5. A. Ryzewska and J. Ryzewski, Reumatologia, 3, 209 (1965).
6. R. H. Wilson et al., in: Conceptual Advances in Immunology and Oncology, New York (1963), p. 521.
7. A. F. Woodhour et al., Proc. Soc. Exp. Biol. (New York), 116, 516 (1964).