When epidermal tumors are induced in mice by a single application of a carcinogen followed by repeated applications of a promoting agent, many of the induced tumors regress in size and eventually disappear (2, 4). The cause for the regression and disappearance of these tumors is not known. They are histologically squamous papillomas and show more pronounced inflammatory changes in their stroma than do permanent tumors (3).

Several general theories can be put forward for the cause of such disappearances. It is possible that these tumors regress because of their inherent genetic nature or the genetic nature of the host animal. It is possible that, of the variety of tumors induced, some are made to disappear by the continuous application of the promoting agent. They may, perhaps, be destroyed by immunological means invoked by an antigen common to many tumors or by individual tumor antigens. An immunological mechanism may be reflected in the inflammatory changes seen in the stroma of the regressing tumors. These tumors are of special interest, since knowing what destroyed them may lead to therapy.

MATERIALS AND METHODS

Tumors were induced in 200 adult, virgin, Swiss female mice by a single application to their shaved backs of 0.1 ml. of 0.5 per cent 7,12-dimethylbenz[a]anthracene (Eastman Organic Chemicals, Rochester, N. Y.) in purified mineral oil (Nujol, Plough [Canada], Ltd). One week later twice-weekly applications of 5 per cent croton oil were begun to the carcinogen-treated area of skin, with a No. 4 squirrel-hair brush. This treatment was continued for 20 weeks. Tumors were observed weekly and recorded on special charts.

RESULTS

Tumors began to appear in significant numbers at week 6, the majority were apparent at week 10, and the first disappearance occurred by week 9. Only tumors observed for at least 3 consecutive weeks were considered, to avoid confusion with inflammatory lesions, since the examination of the mice was solely a visual one. In spite of detailed weekly mapping of tumors, none were seen to recur in areas of previous regressions.

Tumors arising in weeks 6—10 were evaluated first. These tumors had at least 10 weeks to regress; altogether 791 tumors were in this category, of which 272, or 34 per cent, regressed. This rate of regression was like that observed in similar short-term experiments (4), but could have been higher had the animals been observed until death (2). The proportion of regressions was as a function of the time of their appearance was listed in Table 1. The incidence of regressions increased from zero to 47 per cent with time in the 5-week period under consideration.

The proportion of tumors which regressed over the entire length of the experiment as a function of the week of first tumor on individual mice was determined next (Table 2). It was found that mice with earlier-appearing first tumors had fewer regressions than mice with later-appearing first tumors.
Finally, the proportion of regressions among tumors appearing within 10 weeks of the first tumor was tabulated as a function of the week of first tumor (Table 3). In this table were also listed the average tumors per mouse and the average latent periods of tumors arising over the 10-week period. The proportion of regressions rapidly increased from week 6 to week 8 of the first tumor, then became stable till week 10 of the first tumor. The average number of tumors per mouse was inversely related to the week of the first tumor. The average latent period of tumors increased by 0.8 weeks on the average per week of delay in appearance of the first tumor on a mouse.

**DISCUSSION**

Of the various theoretical causes of regressions listed earlier, two do not seem compatible with the results obtained, but no definite conclusions can be made about the others. The inherent genetic nature of the induced tumors is unknown. It is possible that tumors with potentially fewer neoplastic genetic abnormalities would appear later and would regress more often. The results are compatible with this possibility. The Swiss mice used in these experiments are not inbred and are not uniformly susceptible to the induction of tumors (1). The results obtained suggest that less susceptible mice develop their tumors later and have more regressions. This is compatible with the proposition that the genetic make-up of the host contributes to the cause of regressions. If the promoting agent croton oil were responsible for regressions, then the earlier-appearing tumors which were treated with it for a longer time should regress more often than the later appearing ones which were treated with it for a shorter time. The contrary observation was made, and it seems unlikely that the action of croton oil is a major cause of regressions. An immunological destruction of tumors due to an antigen common to all or most of the tumors would be expected to affect more tumors on mice which had earlier first tumors and had more tumors. The contrary was found to occur. This mechanism of regression, therefore, appears unlikely in these chemically induced tumors, although it seems to operate in the virus-induced Shope rabbit papilloma (5). No prediction seems feasible on the probable effects of individual tumor antigens other than that the results seem not to preclude their existence or effect.

The results, therefore, are not compatible with the theory that the continued irritation inherent in the experiment or the immune reaction to an antigen common to all the tumors causes some of the tumors to regress. Other theories discussed remain, alone or in combination, as possible explanations of regressing tumors.

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**REFERENCES**

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