ticum, are the equivalents of sympathetic ganglia or chromaffin cells. If so, it is not surprising that acetylcholine and other ganglionic stimulants excite these structures directly. Dautreband and Maréchal[4] and Wispelaere[5] studied the respiratory stimulating action of various choline derivatives. Wispelaere apparently errs in his statement that mecholyl is a respiratory stimulant, since his tracings reveal that the slight respiratory stimulation which he obtained is due to the steep fall of blood pressure.

We say, in conclusion, that we have shown the existence of a neurohormonal mechanism involving the excitation of the chemoreceptors in the carotid sinus region which, in turn, causes reflex stimulation of respiration. This is a mechanism which may be involved in respiratory stimulation not dependent upon increase in the alveolar carbon dioxide pressure or increase of fixed acids in the blood. In this connection the following paragraph is interesting:[6]

> . . . The pressure of carbon dioxide in the alveolar air is raised during severe exercise, as might be expected, otherwise there would be no stimulus to increase the ventilation; the amount of oxygen lack is usually insufficient to produce it. It has been shown, however, that administration of carbon dioxide in the inspired air can produce a greater rise in the alveolar carbon dioxide pressure than is ever produced in exercise; nevertheless, the ventilation rate is much less than that produced by even moderate exercise. It would appear, therefore, that besides the increase in alveolar carbon dioxide pressure, some factors, as yet unrecognized, may take part in increasing the ventilation rate during exercise.

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SARCOMATA AND CARCINOMATA INDUCED IN COTTONTAIL RABBITS BY METHYLCHOLANTHRENE[1]

THE advantages of the rabbit as a host in which to investigate cancer have become apparent as the result of the study of the carcinoma that follows Shope's virus-induced papilloma in both the domestic (Oryctolagus) and cottontail (Sylvilagus) rabbit.[2] As part of our investigation of this papilloma-to-carcinoma sequence, we attempted to produce malignant tumors in cottontails by the use of methylcholanthrene, a highly potent carcinogenic agent in mice. To this end, we brought the carcinogenic hydrocarbon into prolonged contact with epidermal and mesodermal tissues, with the result that both carcinomata and sarcomata have been produced. Since the rabbit has been generally regarded as comparatively refractory to the action of carcinogenic agents, we have thought it desirable to make our positive results immediately available to the numerous workers engaged in cancer research. Our findings will appear in detail in forthcoming papers. Meanwhile, it should be emphasized that the present note is concerned only with those of our animals which received methylcholanthrene (in its vehicle) alone, *i.e.*, we are not including herein any animals which received both carcinogenic agent and virus.

The cottontail rabbits studied fall into two groups. In Group A, 1 gm of methylcholanthrene was given to each of eleven animals. The carcinogenic agent was injected into each of four sites, two subcutaneous and two intramuscular, in amounts of 250 mg in 1 ml of tricaprylin. This pure saturated triglyceride was used because of Fieser's suggestion[3] that it was desirable to administer carcinogenic hydrocarbons in a solvent with known chemical characteristics. Of the eleven rabbits, six survived for 175 days or more, the rest dying of intercurrent infection or injury. Of the six survivors, five had soft-tissue sarcomas and one an epidermoid carcinoma. The diagnosis was established in each instance by autopsy and histopathological examination. The epidermoid carcinoma, which was discovered on the 176th day, developed at a site of subcutaneous injection. The sarcomata, which were present in rabbits autopsied on from the 225th to the 295th day after injection, were multiple. Metastases had occurred in three of the five animals.

Eight rabbits comprised Group B. Each animal received from thirty-five to forty-two applications of 1 per cent. methylcholanthrene in benzene on the inner aspect of each ear. This treatment extended over a period of from 166 to 220 days. When autopsied from 228 to 362 days after the first application, seven of the eight animals were found to have developed epidermoid carcinomata. In five of the seven rabbits, metastases had occurred—to the lymph nodes in two, and to both the nodes and lungs in three.

The findings described in the present note clearly show that methylcholanthrene is an effective agent for inducing sarcomata and carcinomata in the cottontail rabbit. Its action on the tissues of the domestic rabbit and other hosts is under investigation.

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[4] Dautreband and Maréchal, *C.R. Soc. Biol.*, 113: 76, 1933.

[5] Wispelaere, *Arch. Int. Pharmacodyn.*, 56: 363, 1937.

[6] Winton and Bayliss, "Human Physiology," 2nd edition, p. 181–182.

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[2] For related bibliography, see Peyton Rous, "The Harvey Lectures," Williams and Wilkins Company, 1936, p. 74–115.

[3] Louis F. Fieser, *Am. Jour. Cancer*, 34: 37–124, 1938.