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INDUCTION OF SARCOMAS IN GUINEA PIGS WITH INTRAMUSCULARLY INJECTED SESAME OIL.

BY

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For his guidence in this study I wish to acknowledge my indebtedness to Dr. Harry S.N. Greene, Professor of Pathology.

INTRODUCTION

Reports of spontaneous malignant tumors in guinea pigs have been extremely rare. A survey of the literature in 1937 revealed only 21 such cases (1).

Various attempts have been made to induce malignant neoplasms in guinea pigs in order that wider application might be made of the methods of experimental cancer research previously limited almost entirely to mice and rats.

Most of these attempts have employed administration of carcinogenic polycyclic aromatic hydrocarbons. Prior to 1940 only four reports of induction of malignant tumors in guinea pigs can be found (2). Shimkin and Mider concluded (2): "The impression from the literature, therefore, is that although neoplasms can be induced in guinea pigs following injections of carcinogenic hydrocarbons, the low incidence and the long latent period classify the guiena pig among the animals which are relatively resistant to carcinogenesis with these agents."

In a series of 34 guinea pigs surviving over 18 weeks 29 developed tumors at the site of injection of 20 to 40 mg. of 20-methylcholanthrene dissolved in sesame oil, the tumors becoming palpable in an average of 25 weeks after injection (2).

When Harry S. N. Greene attempted to reproduce this work with 20--methylcholanthrene dissolved in substances other than sesame oil he was unable to do so (3). For this reason the possibility that sesame oil itself might be carinogenic for guinea pigs was entertained.

This possibility was given further credence by the work of Steiner, Stede, and Hock, who obtained sarcomas in 3 of 9 surviving mice injected with sesameoil heated to 350° C. (4). It is interesting to note that no sarcomas were obtained in animals injected with unheated sesame oil.

In May 1950, a patient at the Grace-New Haven Community Hospital was found to have a 5 x 5 cm. mass at the site of injection of two courses of penicillin in sesame oil therapy, one in September 1949 of 7 daily injections, 1 c.c. each, in alternate buttocks; one in February 1950 of 5 daily injections, 1 c.c. each, in alternate buttocks (5). The mass was said to have been present for 6 months. The mass increased in size until at operation in May 1951 it was 10 x 15 cm. Histologically the tumor was a fibrosarcoma. Transplants grew in the anterior chamber of a guinea pig's eye (6). In December 1951 the patient died with metastases to both breasts and both lungs.

In early 1951 another patient at the same hospital was found to have a small mass in the buttock one week after 4 daily injections of 1 c.c. of penicillin on sesame oil into that buttock (5). The mass slowly increased in size until April 1953 it was 15cm. x 15cm. The histological diagnosis at operation was fibrosarcoma. An inguinal node was positive for tumor.

The possibility that sesame oil might be carcinogenic in man added to the previously listed evidence of its carcinogenicity in animals seemed to indicate the desirability of further studies. Thus in November 1953 it was decided to test the carcinogenic properties of sesame oil by the injection of pure sesame oil into the thigh muscles of guiena pigs.

METHODS

Twenty stock guinea pigs of unknown genetic constitution were injected intramuscularly into the right hind thigh with 0.5 c.c. of pure unheated sesame oil. The guinea pigs were of both sexes and of various ages.

Ten of the animals received only the single dose on December 9, 1954. The remaining ten animals received four repeated 0. 5 c.c. doses in the same area at monthly intervals.

The animals were maintained on adequate food and water, and were examined every two weeks for tumor at the site of injection. Between examinations, however, six of the once-injected animals and five of the four-times-injected animals died and were disposed of by the janitor without autopsy. One of the four-times-injected animals was sacrificed at 40 weeks. Four of the once-injected animals and four of the four-times-injected animals were living at the end of one year.

Material for histologic examination was fixed in Zenker's fluid and formaldehyde. It was embedded in paraffin, cut, and stained with hematoxylin and eosin.

RESULTS

About 36 weeks after the initial injection of sesame oil, one of the five surviving guinea pigs that had received multiple injections was found to have a small hard mass at the site of injection. One month later the mass had increased to 2 x 2 cm. in size.

At this time the animal was sacrificed. A firm,gray-white tumor was found at the site of injection,imbedded in the thigh muscle and attached to it, extending through the muscle to lie subcutaneously,but not fixed to the overlying skin. The cut surface was also gray and fibrous. Grossly no necroses was seen.

Microscopically the tumor consisted mainly of two cell types. There were large homogeneous areas of fibrosarcoma with the cells resembling atypical fibroblasts. Adjacent to these areas were other homogeneous areas, much less well differentiated, consisting of fairly large basophilic round cells with centrally placed pycnotic nuclei. Mistoses were common in these highly cellular areas which appeared to be less vascular and contained small necrotic foci. Some sections revealed pleomorphic areas in which many of the cells were intermediate in morphology to the two types of cells described

One year after the initial sesame oil injections, at the time of the writing of this paper, none of the four remaining, live singly-injected animals, and none of the four remaining live multiply injected animals show any evidence of neoplasm.

TRANSPLANTATION

The anterior chamber of the guinea pig's eye was used as the site for two tumor transplants. The technique of transplant has previously been described in detail by Dr. H. S. N. Greene (7). One transplant was made with tumor plus embryonic guinea pig lung, the other with embryonic guinea pig kidney. The embryonic tissues were employed because of their stroma-inducing qualities. It has been recognized that embryonic tissues are exceptional stroma-inducers with an organ-hierarchy of stroma-inducing capacity (3). In this organ-hierarchy embryonic lung ranks as a better stroma inducer than embryonic kidney. Without good stroma the tumor cells cannot receive a blood supply sufficient to support growth.

At three days growth was seen in the eyes of both guinea pigs with transplants. At two weeks the growths filled the eyes of the guinea pigs and they were sacrificied. Microscopic section showed only fetal kidney without tumor cells, inthe guinea pig's eye in which tumor plus fetal kidney had been implanted. In the eye of the animal in which tumor plus fetal lung had been implanted tumor was found to be present. It very closely resembled the undifferentiated round basophilic cell section of the original tumor. Serial transplants were not carried out.

DISCUSSION

The experiment described in this paper was undertaken in an attempt to prove the carcinogenicity of sesame oil for guinea pigs. The fact that a sarcoma had developed in one of the nine guinea pigs living at the end of a year would indicate that sesame oil is a carcinogen for guinea pigs.

The low incidence of tumor induction as compared to the work of Shimkin and Mider, however, requires some explanation (2). Several theories could account for this difference in incidence.

Two possibilities relate to the difference in technique employed. Shimkin and Mider injected two to four times as much sesame oil as was used in this experiment, and they injected it subcutaneously (2). The difference in amount used may be significant. More likely the route of administration is important.

A third possibility is that sesame oil and 20-methylcholanthrene act synergistically in the production of tumors.

Of course, both methylcholanthrene and sesame oil may be carcinogenic for guinea pigs, with methylcholanthrene being more effective, but this theory is highly suspect due to the previously mentioned work of H.S.N. Greene (3).

Still another factor involved is that of the increased

carcinogenicity of sesame oil after heating. It seems significant that as previously mentioned Steiner, Stede, and Koch obtained no sarcomas from mice injected with unheated sesame oil, but that one-third of the mice developed sarcomas after injections of sesame oil which had been heated to 350° C. (4). Some manufacturers heat sesame oil in the production of various products (5). Whether this was done in the production of the 20-methylcholanthrene dissolved in sesame oil used by Shimkin and Mider I do not know (2). Such heating, if it occurred, might profoundly influence the results of the experiment.

The five possibilities listed remain to be investigated.

SUMMARY

In this experiment one out of nine guinea pigs injected with sesame oil developed a sarcoma. Five possible reasons for the low incidence of tumor induction as compared to the incidence obtained by other experimenters using 20--methylcholanthrene dissolved in sesame oil are discussed.

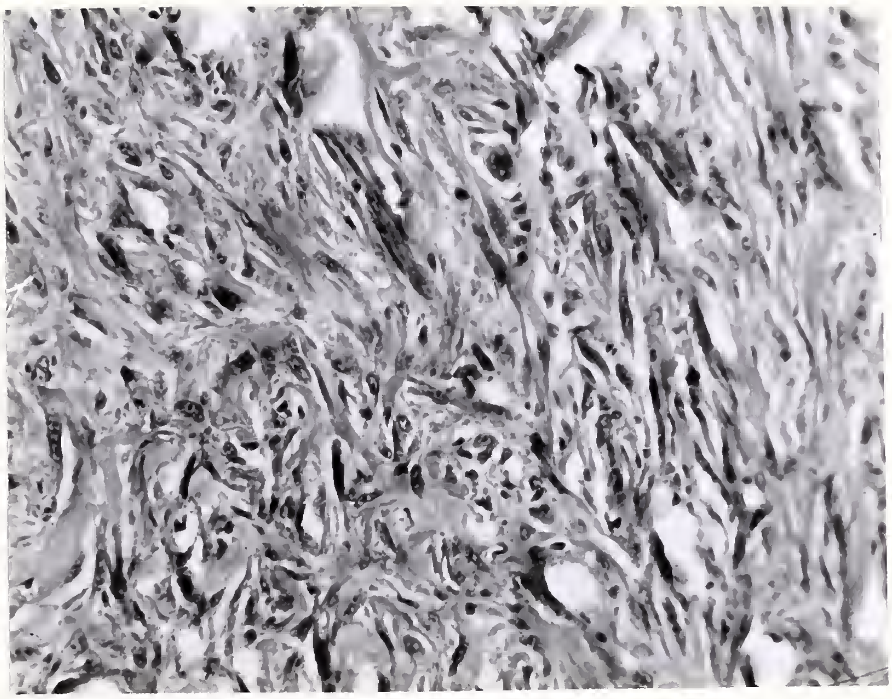

Fig. 1. Sarcoma primary in thigh muscle of guinea pig at site of injection of sesame oil. Note homogeneous fibrosarcomatous nature. x375

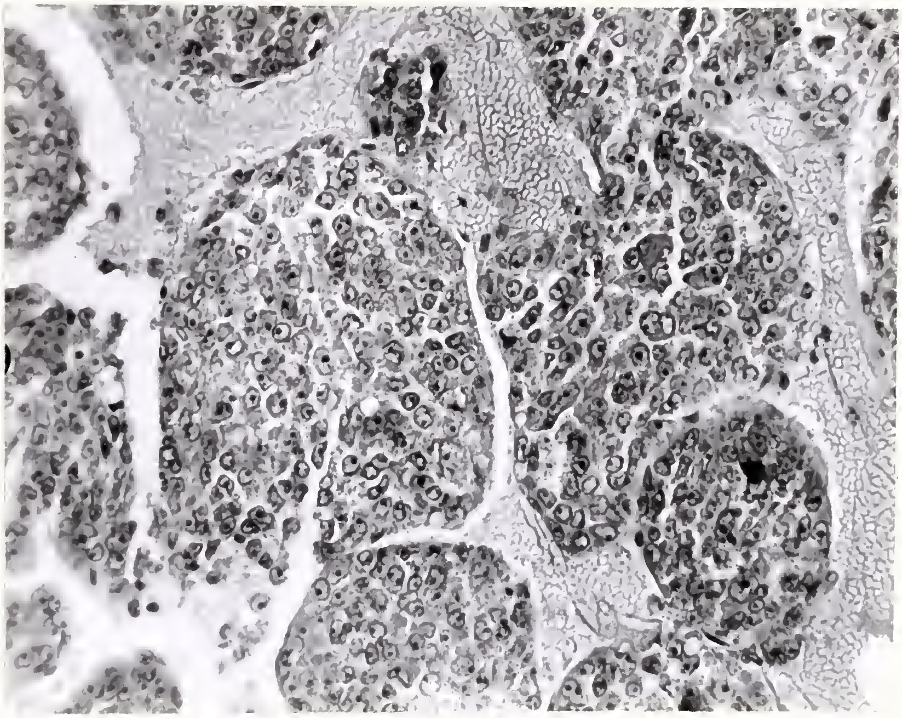

Fig. 2. Another section of tumor shown in Figure 1. Note large round cells with centrally placed nuclei. x375

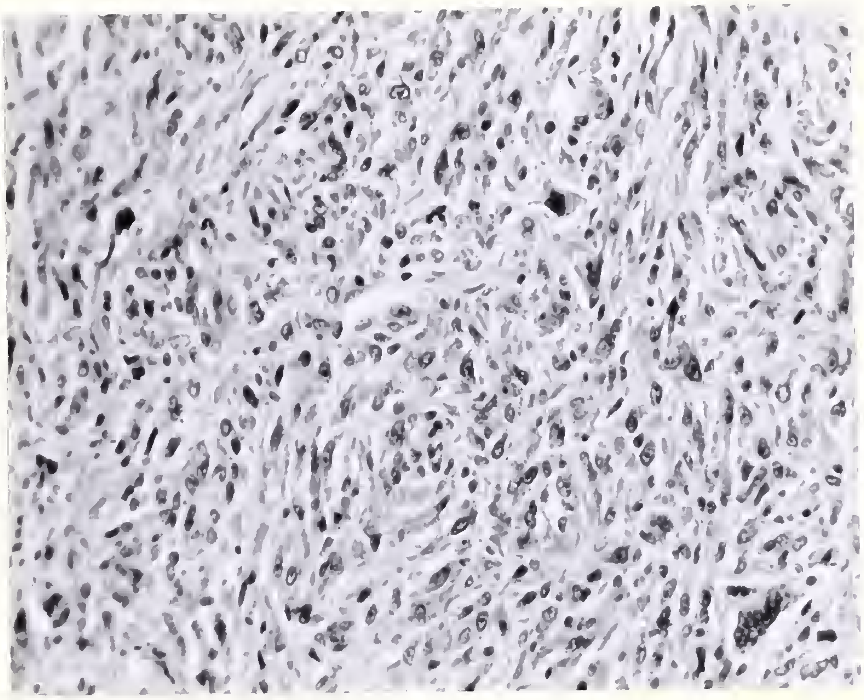

Fig. 3. Another section of tumor shown in Figures 1 and 2. Note pleomorphism. x375

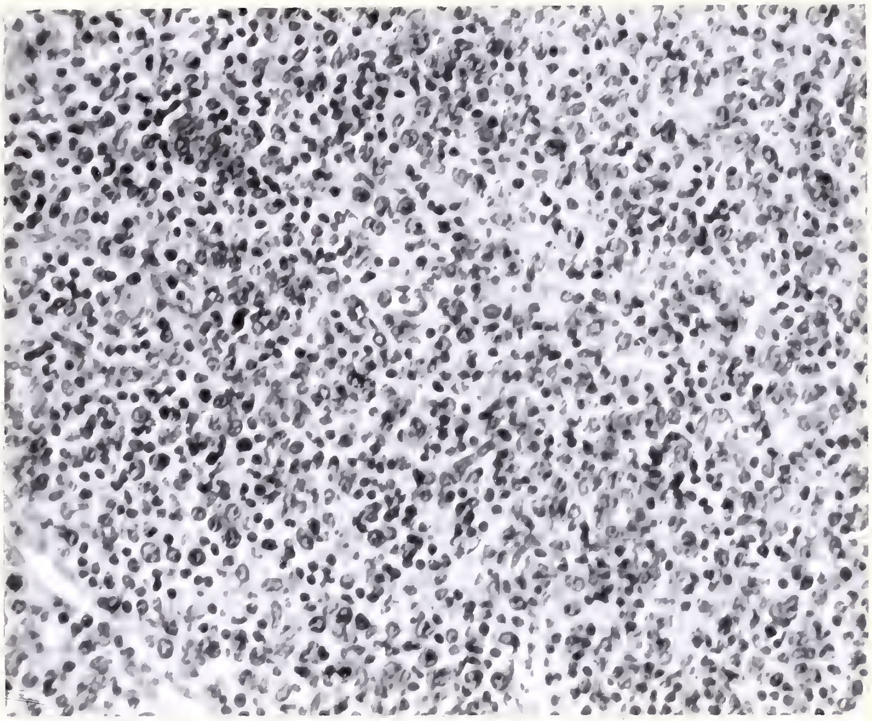

Fig. 4. Anterior chamber transplant of tumor shown in Figures 1, 2, and 3 plus fetal lung. x375

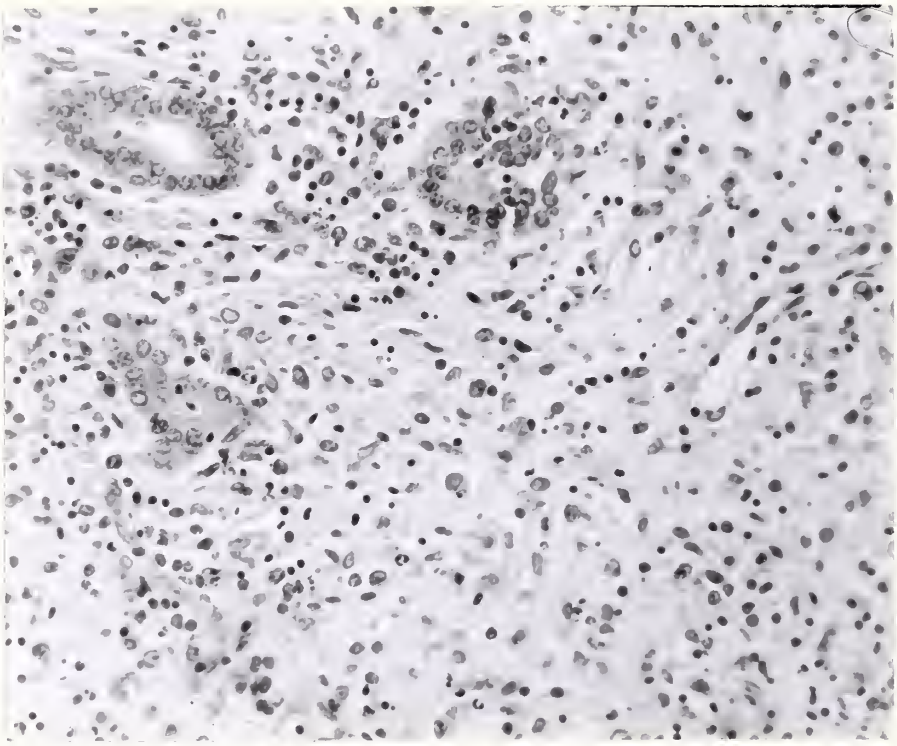

Fig. 5. Anterior chamber transplant of tumor shown in Figures 1, 2, and 3 plus fetal kidney. Note lack of tumor growth. x375

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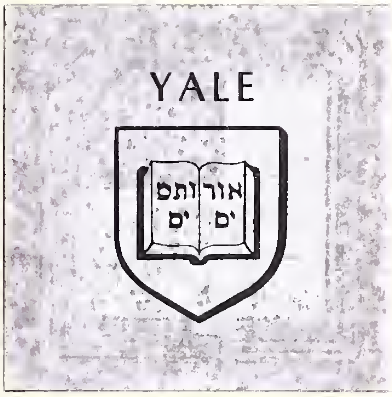
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