cytoplasm. These granules are round, of very constant size and are stained pink by the carmine. They occupy the entire cytoplasm. By means of Altmann's fixative and stain exactly similar granular pictures are obtained.

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The formation of metastases after an intravascular injection of tumor emulsions.

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It is generally accepted that metastasis in malignant tumors is formed by the proliferation of tumor cells which have been transported to distant parts of the organism through the blood or lymph channels. The cells of the primary tumor penetrate in some manner into the lumen of the vessels, are swept away by currents as emboli, and finding lodgment in some distant part of the organism, they proliferate and form secondary tumors.

This conception of the formation of metastasis was established through observation of autopsy material and no direct experimental proof of the matter was adduced up to the present. All experiments with intravascular injection of human tumor material into animals either gave negative results or were entirely untrustworthy.

In all the extensive literature of the last decade on the subject of the transplantable cancer of the white mouse and rat there appears no statement in regard to intravascular injection of tumor material with the aim of forming metastasis. The only exception is a short note by Graf, who obtained negative results.

Metastasis in malignant tumors of the white mouse and rat occurs rarely as compared with human cancer, and the channels for the transportation of the tumor cells are in a majority of cases the blood vessels. The reason for the rare occurrence of metastasis in the rat and mouse Ehrlich, in accordance with his athreptic theory of immunity, sees in the fact that tumors in these animals are usually of extreme malignancy and grow to very large

size. The cells of the primary tumor use up all the specific food found in the organism of the host, and the cells transported from the primary tumor to other regions of the organism do not find the necessary nourishment and consequently can not proliferate. Carl Lewin on the other hand thinks that the fact that metastasis in these animals takes place only through the aid of the blood vessels and not the lymphatics, accounts for the rare occurrence of metastasis in these animals. As was shown by M. B. Schmidt through his observations on human cancer, blood is capable in a majority of cases of destroying cancer cells, found within the blood vessels.

The study of the influence of the blood upon cancer cells carried by it and the capacity of such cells to form metastasis may serve to clear up a number of phenomena in the genesis of cancer. In view of this a systematic study was undertaken by the writers on the experimental formation of metastasis, of which the present communication forms the first report.

The experiments consisted in an injection of a tumor emulsion into the jugular vein or carotid artery of a white rat, and were conducted on three different tumors.

Sarcoma of the White Rat.—This tumor is very malignant, grows to a large size, and the occurrence of metastasis after a subcutaneous inoculation is very rare. In hundreds of animals inoculated by the writers local dissemination was observed not more than in a half dozen cases, and once only was metastasis found in the liver. An emulsion of this tumor was prepared by cutting it in Haaland's mincing machine, grinding in normal salt solution and filtering through a layer of coarse gauze. The milky opalescent fluid contains a sufficient number of living cells to produce a tumor growth after a subcutaneous inoculation. Thirty-six rats received an injection of this emulsion into the jugular vein. The animals were killed at periods ranging from eight days to four weeks after the injection and a thorough search made in all the organs for metastasis. Not in a single instance was a metastatic tumor found. No microscopical study was made of the organs which appeared normal on gross inspection, since this investigation does not concern itself with the question, where the tumor cells circulating in the blood find lodgment, but whether such a

cell transported into a certain organ will form there a visible metastasis. All suspicious nodules found anywhere and all lungs appearing abnormal on gross inspection were examined microscopically with negative results. The same negative results were obtained in six rats, where the injection was made into the carotid artery, and the animals survived. This method is very difficult of execution and the animals usually die a few minutes after the injection from respiratory paralysis, while the heart continues its action a few minutes longer.

Carcinoma of the White Rat (Flexner-Jobling).—This tumor is not as malignant as the previous one, but metastasis occurs frequently after a subcutaneous inoculation. The metastasis is usually found in the lungs, but it was also observed by Flexner and Jobling in the kidney, the heart and even in the lymphatic glands, though the authors believe that in most cases the metastases were produced through the blood current. Sixteen rats received an injection of an emulsion of this tumor into the jugular vein. In three animals metastasis was found in the lungs, no other organ showed any metastasis. Six rats survived an injection into the carotid and of these animals one showed metastasis in the lungs. In another rat, in which the injection was made in the carotid against the stream of blood, the animal was found dead twelve days later. At the autopsy a nodule was found on the wall of the left ventricle. The animal remained dead in the cage over night and the specimen had greatly deteriorated, still the nodule resembled microscopically the picture described by Flexner and Jobling of a metastasis found by them in the heart.

Sarcoma of the White Mouse.—Ehrlich has shown, that when this tumor is inoculated subcutaneously into a rat, there forms a small nodule, which remains for 8–10 days, and is then absorbed. No metastasis formation of this mouse tumor into a rat was ever noted. An emulsion of this tumor was injected into the jugular vein of twelve rats. The rats were killed in periods of 4–8 days and in two of the animals metastatic nodules were found in the liver. Neither in the lungs nor in any other organ was there found any metastasis.

The results of these experiments seem to indicate in accordance with the opinion of M. B. Schmidt, that cancer cells introduced

into the blood circulation in a majority of cases lose their proliferating power. Ehrlich's opinion that the most virulent tumors do not form metastasis also seems to be correct, as no metastasis was formed after the injection of the most virulent sarcoma of the rat. But the athreptic theory does not explain this fact. None of these animals had any sarcoma growth anywhere and consequently the sarcoma cells introduced into the circulation could find all the necessary specific food.

The most interesting phenomenon observed in the course of these experiments consists in the fact, that while the Flexner tumor found lodgment in the lungs after an intravascular injection, the mouse sarcoma produced metastasis only in the liver. It would seem that the different topographic distribution of metastasis in the different kinds of malignant tumors is due not so much to the difference in the channels through which the cancer cells are transported, and which were identical in all experiments reported here, but to a specific affinity between cancer cells and cells of certain organs. The comprehension of this specific affinity between a cancer cell and a particular part of the organism of the host may be helpful in elucidating many factors in the genesis of tumors and will be the main object of the further study of the experimental metastasis formation by the writers.