The Fate of Circulating Tumor Cells

II. A Mechanism of Cortisone Action in Increasing Metastases*

IRVING ZEIDMAN

(Department of Pathology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania)

SUMMARY

Studies of effects of cortisone on metastasis were made with the Brown-Pearce carcinoma in domestic rabbits. Suspensions of tumor cells were injected intravenously into normal and cortisoneized animals. Cortisoneized animals developed more metastases than did the controls. Further experiments were done to determine whether cortisone increases metastases by promoting arrest of tumor cell emboli. Tumor cell suspensions were injected into mesenteric arteries of normal and cortisoneized rabbits. Simultaneously, microcinematographic studies were made of tumor cell emboli arriving in mesenteric capillaries. More tumor cell emboli were permanently arrested in the mesenteric capillaries of cortisoneized rabbits. Capillary and tumor cell diameters in cortisoneized animals were not different from those in the controls. Thus, differences in the incidence of embolic arrest did not depend on a disparity in size of tumor cell and capillary lumen.

It is concluded that cortisone increases the number of metastases and also increases the incidence of arrest of tumor cell emboli. Cortisone may increase metastases by promoting embolic arrest, since arrest of tumor emboli is necessary for the development of metastases.

Metastases can develop only after arrest of tumor cell emboli. Some blood-borne emboli can recirculate (4–7, 9–11). Probably such emboli are not sources of metastases unless they are arrested ultimately in sites favorable for their development (3). This report concerns the effect of cortisone on arrest of tumor cell emboli. Past investigations have shown that cortisone increases metastases (1, 2). Cortisone may promote metastases by increasing the incidence of arrest of circulating tumor cells. Experiments were developed to test this hypothesis. With microcinematographic techniques it was possible to count the number of tumor cells passing through or arrested in a capillary bed.

MATERIALS AND METHODS

The transplantable Brown-Pearce carcinoma was used in domestic rabbits. Tumor cell suspensions were prepared by passing pieces of tumor through a sieve into balanced salt solution and serum. Clumps were removed by centrifugation. The mesentery of an anesthetized rabbit was removed and fixed in a special chamber (9). A suitable arterio-capillary field was viewed with a microcinematographic apparatus. Then a dilute suspension of single tumor cells was injected into the mesenteric artery, and, simultaneously, photographs were made of the tumor emboli arriving in the capillary bed. Experiments were done in normal and cortisoneized rabbits. The latter received 50 mg. of cortisone acetate, Merck, intramuscularly, 16 hours before the experiment. All rabbits were saved after microcinematographic studies and then sacrificed 2 weeks later. The mesenteries which had received injections revealed tumor growth, often in the form of miliary surface nodules, in over 95 per cent of the cases.

RESULTS

Effect of cortisone on number of metastases.—Before testing the action of cortisone on embolic
arrest in rabbits, it was necessary to determine whether cortisone increases metastases in rabbits as it does in mice. Forty cortisonized and 30 normal rabbits were given injections intravenously of 1.0 cc of a suspension of Brown-Pearce carcinoma cells. Each rabbit received 160,000 tumor cells. All rabbits were sacrificed 2 weeks later. Counts of lung metastases were made, and the degree of metastatic involvement of liver and kidney was estimated. The mean number of lung metastases was 603 in cortisonized animals (range, 52–2350) and 193 in normal animals (range, 12–38%). The difference in means was significant (P < .01). The number of metastases in liver and kidneys was generally proportional to that in the lungs. Thus, cortisone increases the number of metastases from the Brown-Pearce carcinoma in rabbits.

Effect of cortisone on incidence of arrest of tumor cell emboli.—Suspensions of Brown-Pearce carcinoma cells were injected into the mesenteric artery of rabbits, and, simultaneously, microcinematic studies were made of the mesenteric capillaries. The number of cells arrested or passing through the capillaries into the venules was determined. In normal rabbits most of the tumor cells passed unarrested through the capillary circulation. In twenty such experiments a total of 58 cells arrived at the arterio-capillary junction. Only three cells were permanently arrested, and the other 55 cells passed through the capillaries immediately (Fig. 1). This result contrasted sharply with that obtained in cortisonized rabbits. In eighteen experiments with cortisonized rabbits, 23 of 52 cells were permanently arrested (Fig. 2). Thus, cortisone increased the incidence of permanent arrest of circulating tumor cell emboli.

Measurements of cells and vasculature.—Is increased embolic arrest in cortisonized animals secondary to capillary constriction? To answer this, the diameters of the capillaries in photographed mesenteric fields were measured. The mean capillary diameter in cortisonized rabbits was 11.3 μ, whereas the mean capillary diameter in normal rabbits was 10.4 μ. These figures were not significantly different. Thus, the cortisone effect was not attributable to capillary constriction.

Nor was the cortisone effect due to an accidental preponderance of larger cells in experiments with cortisone. The mean size of the tumor cell in cortisonized rabbits was 17.7 μ, whereas the mean cell size in normal animals was 17.8 μ. No significant difference in size of tumor cells was found.

DISCUSSION

It is generally believed that arrest of a tumor cell embolus depends on a disparity in size between the embolus and the recipient vessel. Explanations of distribution of metastases are based almost exclusively on the concept that the first arterio-capillary filter bed met by the blood-borne embolus is the expected site of lodgement (8). Such considerations seem irrefutable when applied to large, multicellular emboli. However, not all circulating single tumor cells are arrested immediately in the peripheral vascular bed of the first organ encountered (9–11). Large tumor cells can elongate in narrow capillaries and so pass unarrested into venules (9). The factors responsible for the arrest of single tumor cells need elucidation for a better understanding of the genesis of metastasis.

The demonstration of increased metastases following cortisonization suggested the possibility that a humoral factor may be operative in the lodgement of circulating tumor cells. Support for this concept was obtained in the above experiments. Cortisone increased the incidence of embolic arrest. This action could account, at least in part, for the observed increase in metastases produced by cortisone, since arrest of tumor cell emboli is essential for the formation of metastases.

Why does cortisone promote the arrest of circulating tumor cells? Measurements of capillary diameters indicate that vasoconstriction is not responsible for the observed cortisone effect; nor is it likely that cortisone, by increasing the rigidity of the tumor cell, prevents conformation of the cell to the narrower capillary lumen. In the above experiments the cells were photographed soon after

![Fig. 1a–b.](image-url) Transcapillary passage of Brown-Pearce carcinoma cell in normal rabbit. In 1a, the cell is dumbbell-shaped, as it distorts around an arterial “shell” to gain access into capillary. In 1b, the cell has already passed through the capillary, and the arterial “shell” is evident.

![Fig. 2.](image-url) Permanent arrest of Brown-Pearce carcinoma cell in a cortisonised rabbit. The tumor cell maintained its position in the capillary during the entire experiment lasting half an hour.
injection into the artery. Cells did not contact the rabbits' plasma for any appreciable time. It is possible that cortisone may favor embolic arrest by increasing the stickiness of capillary endothelium. Present work is aimed at testing this concept.

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REFERENCES

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Irving Zeidman


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