Immediate Passage of Tumor Cell Emboli through the Liver and Kidney

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This report is one of a series dealing with the passage of tumor cell emboli through the circulatory bed of various organs (6). The problem is to determine whether or not tumor cells, circulating in the blood, may pass immediately through an organ, perhaps to lodge in a more distant organ. If so, this might account for some peculiarities in the distribution of metastases. For example, human cancers of the gastrointestinal tract occasionally metastasize to lungs without producing visible liver metastases (5). Previously, it has been thought that this pattern of metastasis depends upon lymphatic and thoracic duct spread. However, it is possible that tumor cells have passed via the portal vein to the liver, traveled through the liver, and finally lodged in the lungs. The following experiments were designed to ascertain whether immediate passage of tumor cell emboli through the liver and the kidney could be shown.

MATERIALS AND METHODS

The tumors used were the transplantable V-2 squamous-cell carcinoma in rabbits, and the Flexner-Jobling carcinoma, Lewis fibrosarcoma #4, Murphy-Sturm lymphosarcoma, and Lewis lymphoma in rats. Suspensions of cells were prepared by pressing fragments of tumor through a sieve and collecting the cells in balanced salt solution and serum. To determine if tumor cell emboli passed through the liver, a suspension of cells was injected into the portal vein while blood was withdrawn simultaneously from the vena cava just above the liver. This blood was then injected intravenously into a second animal. Tumors developing in the second animal would mean that immediate transhepatic passage of tumor cells had occurred in the first animal. Similarly, tests were performed on the kidney. Tumor cell suspensions were injected into the aorta above the renal arteries, while blood was collected from the renal vein.

For each experiment 1–3 cc. of tumor cell suspension was used. Counts of tumor cells ranged from 800 to 12,800/cc mm. The larger volumes and more concentrated suspensions were used in rabbits. The volume of blood withdrawn from the liver was 40 cc. in rabbits and 1.5 cc. in rats; from the kidney 10 cc. of blood was withdrawn in rabbits, and 1.5 cc. in rats. In these experiments it was necessary to insert and maintain the position of two needles, each in a separate vessel, within a narrow field. To do this, wire clamp attachments were devised (Fig. 1).

RESULTS

Immediate transhepatic and transrenal passage of tumor cell emboli occurred in both rabbits and rats with all tumors tested except the Flexner-Jobling carcinoma. In this experiment one rat received tumor suspension in the portal vein while blood was withdrawn simultaneously from the vena cava above the liver. This blood was then injected intravenously into a second normal rat. Three weeks later the second rat was sacrificed, and the lungs revealed tumors, as shown in the photograph. An example of immediate transhepatic passage of tumor cell emboli. Hematoxylin and eosin. X140.

Fig. 1.—Needles with wire attachments used to hold needles in place inside vessels during transhepatic passage studies in rats. The left needle is used for portal vein injection, and the right for withdrawal of blood from the vena cava. The wire clamp of each needle has a concave fold which tightly embraces the shaft of the needle near the tip. The fold is pulled free from the shaft by setting the wire, and then the needle is inserted into the vessel. The wire is then released, and the fold snaps back against the shaft of the needle, trapping the vessel wall between. Polyethylene tubes, not shown, are glued into the socket of each needle. X1.5.

Fig. 2.—Lung of rat showing growth of tumor, Lewis fibrosarcoma. In this experiment one rat received tumor suspension in the portal vein while blood was withdrawn simultaneously from the vena cava above the liver. This blood was then injected intravenously into a second normal rat. Three weeks later the second rat was sacrificed, and the lungs revealed tumors, as shown in the photograph. An example of immediate transhepatic passage of tumor cell emboli. Hematoxylin and eosin. X140.

Fig. 3.—Rat liver showing Murphy-Sturm tumor cells. In this experiment one rat received tumor suspension in the aorta above the renal arteries, while blood was withdrawn simultaneously from a renal vein. The blood was then injected intravenously into a second normal rat. This second rat was sacrificed 8 weeks later, and the microscopic picture of its liver is shown. Tumor cells are seen in the intralobular vein, sinusoids, and liver cords. A positive example of immediate transrenal passage of tumor cell emboli. Hematoxylin and eosin. X280.
Jobling (Table 1, Figs. 2, 3). The incidence of such passage varied. The solid tumors, V2 carcinoma and Lewis fibrosarcoma, showed uniformly low incidences of passage through both liver and kidney. In contrast, experiments with lymphoma tumors were frequently positive. Murphy-Sturm lymphosarcoma cells passed through both organs immediately in about 70 per cent of tests. This figure is perhaps lower than it otherwise might be, because this tumor regresses spontaneously in about 30 per cent of animals (4). The Lewis lymphoma cells passed through the liver in every experiment. Thus, tumor cell emboli can pass unarrested through the circulation of liver and kidney, and the frequency of this passage apparently depends in part on the type of tumor cell.

**DISCUSSION**

Even a low incidence of organ passage, as found with solid tumors, becomes significant in light of the experimental method. In preparing the tumor suspension by pressing tumor fragments through a sieve, many tumor cells are damaged or killed (7). The intravenous injection of a tumor cell suspension leads to the development of far fewer tumors than the number of cells injected (7). In transhepatic experiments, withdrawal of blood from the vena cava instead of hepatic vein probably leads to a considerable loss of tumor cells which traversed the liver circulation immediately. In spite of these obstacles, immediate passage of tumor cell emboli was demonstrated in both rats and rabbits. It would seem probable that such passage may occur also in man.

Heretofore, it was commonly accepted that an abdominal organ would arrest tumor emboli upon arrival, and metastases would first appear in this organ. Then these metastases may often release tumor emboli to form new tumors in a second organ. The present experiments show that tumor cells are not always arrested in the capillary bed of the first organ, but may pass through the organ at once and thus are free to produce metastases in a distant location.

Experiments with the lymphomas have different implications. These rat lymphomas, like human lymphomas, frequently progress from local growths to fatal leukemias (1-8). Apparently, once the blood stream is invaded by the lymphoma cells, the latter circulate a long while, thereby producing the marked leukocytosis characteristic of leukemia. The above experiments, showing a high incidence of immediate passage of lymphoma cells through organs, tend to favor this concept.

**SUMMARY**

Experiments were done to ascertain whether or not tumor cell emboli could pass unarrested through the liver and kidney. The transplantable V2 carcinoma was used in domestic rabbits and, in rats, transplantable Flexner-Jobling carcinoma, Murphy-Sturm lymphosarcoma, Lewis fibroma, and Lewis lymphoma. For transhepatic studies, tumor suspension was injected into the portal vein, and simultaneously blood was drawn from the vena cava just above the liver. The blood was then injected intravenously into a second animal. The development of tumors in the second animal indicated immediate transhepatic passage of tumor cell emboli in the first animal. In transrenal studies, tumor suspension was injected into the aorta above the kidneys, the blood was collected simultaneously from the renal vein, and this blood was injected intravenously into second normal animals.

**REFERENCES**

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