Metastasis: A Review of Recent Advances*

IRVING ZEIDMAN

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

Lately there has been a revival of interest in the problems of cancer metastasis. This renewed interest arose when attention, no longer centered on autopsy and morphological observation, turned to experimental methods. With adoption of the experimental method it was possible to explore the underlying mechanisms and dynamics of metastasis. Older concepts, derived from examination of dead human tissues, were re-examined, confirmed in some respects, altered or rejected in others.

Accordingly, the aim of this review is to present the results of these recent experimental studies. The purely morphological aspects have been reviewed elsewhere (44, 48) and are not included here.

By metastasis of neoplasms is meant the presence and growth of a tumor in a part of the body distant from its original location. This secondary tumor arises as the result of transportation of tumor cells to a new location by either the blood stream or the lymphatics, or by transport in coelomic cavities.

BLOOD-BORNE METASTASIS

The development of a metastasis involves three major steps. (a) Invasion: cells of the primary tumor migrate into surrounding tissues and penetrate the walls of blood vessels. (b) Embolism: tumor cells break loose inside vessels and are carried to distant parts. Here the cells are arrested in capillaries or arterioles. (c) Development of arrested emboli: cells of the arrested embolus multiply, invade the vessel wall, and infiltrate adjacent tissues. Concurrently, a vascularized stroma grows from the local tissues and supports growth of the tumor cells. Thus, a new tumor forms in a distant site, a metastasis.

1. INVASION

Unless tumor cells are able to invade, that is, push into surrounding tissue, they cannot force their way into blood vessels. Therefore, without invasion metastasis cannot occur. Invasiveness was investigated especially by Coman et al. (14). They showed that a major factor enabling cancer cells to become invasive is their decreased adhesiveness (13, 36)—i.e., cancer cells are only loosely attached to one another, they separate easily, and migrate into the surrounding tissue by means of their own active ameboid motility (12). One reason for their decreased adhesiveness is that cancer cells are deficient in calcium (8–11, 19, 20, 51). Since, in any cell, calcium lies chiefly at the cell surface (26), a defect in the surface of the malignant cell was suspected. Accordingly, the ultramicroscopic structure of the surface was observed and compared with that of normal cells (15, 16). Definite irregularities were found in the macromolecular surface structure of cancer cells, as would be expected if their surfaces were defective. These structural abnormalities may account for their reduced adhesiveness which is the basis of invasiveness.

Invasiveness in relation to heterologous transplantation.—There appears to be a correlation between invasiveness and heterotransplantability. Greene has reported that human and animal tumors, when transplanted into the eye or brain of alien species, “take” and grow usually if the tumor has already metastasized in the original host (25). This means that the tumor cannot survive in the alien host unless it has already developed a high degree of invasiveness, particularly of blood vessels.

2. EMBOLISM OF TUMOR CELLS

In the course of their invasion of surrounding tissue, tumor cells penetrate blood vessels. It is chiefly the veins that are invaded, rarely arteries, since arterial walls interpose a barrier that is generally effective, whereas the walls of veins are readily permeable (48, p. 15). Once inside the vessel, cancer cells may be swept away in the venous stream, or they may linger locally and multiply. In many instances a thrombus forms around the tumor cells. Pieces of the thrombus may break off and, laden with malignant cells, be carried to and lodge in distant organs.

* The reported investigations of the author were supported by grants from the Division of Research Grants and Fellowships of the National Institutes of Health, U.S. Public Health Service (Grant #C-4556), and the Anna Fuller Fund.

Received for publication November 30, 1956.
It is likely that embolism occurs repeatedly, since the number of metastases tends to increase with time. In other instances, showers of emboli are probably emitted, as is evidenced by finding a lung or liver studded with deposits of almost equal size. It seems possible that a sudden change in venous pressure, as may occur in coughing, may dislodge many cancer cells and send them floating in the blood stream. Such multiple coincident embolism is duplicated experimentally, when quantities of tumor cells are injected intravenously. Embolism is duplicated experimentally, when quantities of tumor cells are injected intravenously, and the result is the same as is sometimes seen in human malignancy; many metastatic nodules of similar size appear in the lung or liver.

Passage of tumor cell emboli through organs.—It was formerly believed that nearly all tumor cell emboli released into veins were arrested in the vascular network of the first organ encountered, and that here the earliest metastases developed (48, p. 45). This concept has clinical support in that metastases are most frequently observed in lungs, liver, and bones, as would be expected on anastomoses and arteries. Metastases in other organs were believed to be derived from tumor emboli released by the first set of metastases (48, p. 175). The possibility that some tumor cells might pass immediately through the circulation of an organ was generally disregarded, save perhaps for small sarcoma or lymphoma cells (44, p. 117). This concept needs some revision in view of recent experimental work. With transplantable tumors in rabbits and rats it was demonstrated that some tumor cells of carcinomas and sarcomas pass immediately through the circulation of lung, liver, spleen, and kidney (32, 53, 56). Ascites tumor cells evidently recirculate for long periods of time (2, 30).

Furthermore, the frequency of such passage through an organ varies, depending on the type of tumor cell. Thus, in rabbits, Brown-Pearce carcinoma cells pass through the lungs frequently and Vt carcinoma cells infrequently (53). This difference in incidence of immediate passage correlates well with the spontaneous behavior of these tumors. The Brown-Pearce tumor, growing in muscle, tends to metastasize to many organs besides the lungs (21). The Vt carcinoma, under similar conditions, spreads to the lungs occasionally but rarely to organs downstream from the lungs. These observations suggest that many metastases in organs beyond the lungs originate from tumor cell emboli that have passed unarrested through the pulmonary circulation.

The mechanisms involved in the passage of tumor cells through the vascular beds of organs are not known. Passage through arteriovenous anastomoses cannot be the only explanation. Other factors must play a part, because the two types of rabbit tumor cells pass through the lung to a different degree even under similar experimental conditions (53). These experiments also suggested that the size of the tumor cell is not necessarily the most important factor in passage. The tumor showing a higher incidence of passage was composed of larger cells. Then ascites tumor cells, which appear to circulate freely (2, 30), are relatively enormous. An in vivo study of the behavior of tumor cells upon reaching the capillary bed might reveal how immediate passage takes place. It is conceivable that ease of passage is associated with plasticity of the cell in the capillary lumen.

The demonstration that tumor cell emboli may pass through organs is of clinical interest in explaining unusual distributions of metastases. For example, secondary tumors may be absent from the lungs but present in organs farther downstream. In the past, such a situation has been explained by assuming that tumors were in fact present in the lungs, but were missed because of their small size (48, p. 45). An alternative explanation is that embolic tumor cells passed immediately through the lungs so that no metastases developed there.

3. Development of Arrested Emboli

Tumor cell emboli usually lodge in the small vessels of an organ. Some arrested emboli develop, but the majority succumb (28, 40, 45, 47, 57). Development of the emboli into metastases occurs by multiplication of tumor cells, their invasion into the vessel wall and neighboring parenchyma, and by concurrent ingrowth of vascularized stroma from the local tissues. These events have been depicted by a combination of experimental and histological studies (5, 28, 48, 45). An in vivo study of this process is lacking and may give additional information.

Effect of hormones on metastases.—Recent work indicates that humoral factors may affect the growth of tumor cell emboli into metastases. Thus, Agosin et al. (1) observed that transplanted mammary carcinoma in cortisone-treated mice produced widespread metastases, but no metastases appeared in untreated mice. Similar results were obtained with other transplantable or induced tumors (3, 50), and several tumors did not respond to cortisone in this fashion (29, 35). It was first thought that cortisone increased the number of metastases by its local action on the connective tissues around the primary tumor, leading to greater release of tumor emboli (1).
However, further work indicated that cortisone acts on the tumor emboli after they have lodged. Thus, Baserga and Shubik found that cortisone increased the number of lung metastases even if injected after the primary transplant was excised (4). Pomeroy found that Krebs-2 cells injected intravenously in mice led to lung metastases only, but, if cortisone was administered, metastases developed in many abdominal viscera (38). Probably this effect did not depend on immediate transpulmonary passage of emboli, since injection of cells into the left ventricle led to the development of tumors in many organs of cortisonized animals but in only a few organs of the noncortisonized controls. The action of cortisone, therefore, was either on the tumor cell emboli or on the organs in which they lodged.

Following an intravenous or intraperitoneal injection of ascites tumor cells, a microscopic examination of abdominal organs reveals these large cells free in vascular channels. Yet, these tumor cells never develop into metastases in abdominal organs of the host under such conditions. With cortisone, metastases do develop. The mechanism of action of cortisone in this instance is not known.

There is little information available on the effects of other hormones on the development of metastases. Wood et al. (49) demonstrated that pituitary growth hormone increased the number of lung tumors in mice following intravenous injection of a suspension of tumor cells, but the hormone had no effect on the number of spontaneous metastases from a local tumor. Thyroid-stimulating hormone was ineffective. The association of pregnancy and increased metastases suggests a humoral effect (47, p. 246, 49).

Sites of metastases.—Many tumor cell emboli are arrested in the vascular bed of the first organ encountered, as judged by the distribution of secondary tumors. The lungs and liver are the most frequent sites (48, p. 179), because most of the venous blood drains into these organs. Secondary tumors are also common in the bones (48, p. 239), probably because tumor emboli in veins may reach the bones directly via Batson’s plexus under conditions of increased intra-abdominal pressure (6, 7). Experimental work has demonstrated that tumor cells in veins may reach the bones without first going through the lungs and, once in bones, may lodge and develop into metastases (17, 37).

It is easier to account for the frequent sites of metastases than for the infrequent ones. Why is it that metastasis occurs so infrequently in such organs as muscle, spleen, and thyroid (47)? The answer to this question was sought by Coman et al. (18). Tumor cell emboli, when injected into the left ventricle, were trapped in the arterioles of spleen, thyroid, and muscle, whereas in other organs the cells lodged in the capillaries. The number of metastases that subsequently developed was proportional to the number of cells reaching the capillary bed of the organ. Metastases do not develop frequently in muscle, spleen, and thyroid because the arterioles arrest the emboli. Apparently tumor cells have as much difficulty in escaping from arterial structures as in entering them.

The coincident and ensuing experimental work in part supported these conclusions, but also indicated the need of modifying or expanding them, and this was true especially as regards the lungs. Thus, Lucké et al. (34) found that simultaneous injection of tumor cell suspensions into the pulmonary and hepatic circulations produced more tumors in the liver than in the lung. Evidently, there is some factor in the lungs unfavorable to tumor growth; it may be their continual motion, high degree of aeration, or some unrecognized chemical factor.

Sugarbaker’s work, at least ostensibly, indicates that mechanical factors are not alone in determining the distribution of secondary tumors (42). He injected suspensions of cells from various kinds of tumors into the left ventricle of rats and observed the sites of metastasis at death. Each type of tumor had established its own pattern of metastasis. Whether unrecognized mechanical factors or local chemical conditions were responsible for these differences is not known. The same considerations apply to similar experiments with ascites tumors (38).

It was previously stated that embolic tumors establish themselves in capillaries, but rarely in arterioles. In this regard the lung is an exception. In spontaneous pulmonary metastases of a mouse sarcoma, Baserga and Sabbioni (6) found that one-third of the tumors had grown out of arteries and their branches, though the majority appeared to have grown from capillaries. Perhaps the lung arterioles are unique in their penetrability by cancer cells, though precise information is lacking.

SPREAD VIA LYMPHATICS

Much of our recent knowledge concerning the mechanism of lymphatic spread of cancer was made possible by experiments in which tumor cells were injected directly into afferent lymphatics (52, 54, 55). In this way it was possible to test the effectiveness of the lymph node as a
barrier to the spread of cancer. Transplantable carcinomas were used in rabbits. It was found that tumor cell emboli are arrested in the subcapsular sinus of one or more lobules of the lymph nodes, and here early growth occurs. The cancer is contained by the node for at least several weeks after emboli are first arrested and usually for a longer period of time (54), so that spread of cancer from node to node occurs only after a considerable delay.

The lymphatic supply of carcinoma.—Experiments were performed to determine if cancer has a lymphatic supply (55). Intralymphal tumor growth in rabbits was produced by injection of tumor cell suspension into afferent lymphatics, and 2 weeks later tracer substance in the form of radiogold or dye was injected into afferent lymphatics of the same node. Then appropriate studies were made to locate the tracer in the cancerous node. It was found that the tracer spread well in the lymphatic tissue but did not penetrate the cancer nodule. Even when the injections were made under high pressure the tracer did not penetrate the tumor. Hence, no lymphatic supply could be demonstrated within the tumor. Experiments with other cancers have also failed to reveal lymphatic vessels in any of the tumors tested (22, 24, 27, 39, 41, 46).

Clinically, radiogold is injected around the primary cancer in the hope that it will be carried through the lymphatics to the lymph nodes where metastases may exist. However, the effective irradiation distance of radiogold is only 1–2 mm. Lacking lymphatics, a cancer nodule could not be penetrated by radiogold, and only a small cancer nodule or recently arrived tumor cell emboli could be irradiated effectively.

The spread of tumor cells in the thoracic duct.—With the above experimental approach it was also possible to find what happens to tumor cell emboli in the thoracic duct (52). Previously, it was believed that all emboli in the thoracic duct go to the neck veins and thence to the lungs. However, by injecting cells of transplantable tumors into the thoracic duct of rabbits, it was found that some emboli in the duct passed directly to nearby lymph nodes, the mediastinal and intercostal. Early tumor growth in these nodes was chiefly in the subcapsular sinus region, suggesting that the cells had reached the nodes through afferent lymphatics from the thoracic duct. Branches between duct and nodes were found when a dye was injected into the thoracic duct of the normal rabbit. Similar branches were found in a human fetus, and the left supraclavicular node was stained by the injected dye. This result suggests an explanation of Virchow's node (48, p. 33). It would seem that Virchow's node is due to tumor cell emboli which reach the supraclavicular node from the thoracic duct via direct pathways.

Numerous questions regarding the spread of cancer in the lymphatic system remain unanswered. What is the mechanism of the retrograde lymphatic spread of cancer, as occasionally observed? How effective is the lymph node as a barrier to the passage of sarcoma and leukemia cells? Properly designed experiments should solve these problems.

METASTASIS BY IMPLANTATION

The third method of metastasis involves release of tumor cells or fragments into cavities with subsequent implantation and growth on serosal or mucosal surfaces. Investigative work on this aspect of metastasis has been stimulated recently by the extensive use of ascites tumors. Thus, Goldie injected identical doses of tumor cells subcutaneously, intrapleurally, and intraperitoneally and found that intrapleural injections produced death earliest (23). When ascites tumor cells are introduced into the peritoneal cavity some of them soon get into the blood stream, indicating that the peritoneal barrier is not effective against single cells (30).

Chromosome counts of human tumor cells in ascitic and pleural fluid reveal considerable variation, although the majority range around the diploid number (31). This indicates that metastatic cells have the same genetic constitution as those of the primary tumor, contrary to results obtained by indirect experiments using DNA measurements of metastatic cancers (33).

SUMMARY

Recent developments in research on metastasis have been reviewed. The process of metastasis begins when cells of the primary cancer invade surrounding tissues. At least one major factor responsible for this invasion is decreased adhesiveness of cancer cells, a property associated with deficient calcium and macromolecular abnormalities on the cell surface. Because of decreased adhesiveness cancer cells can separate from each other, move into surrounding tissues, and penetrate vessels. Following vascular invasion, tumor cell emboli are discharged into the blood stream. Most of these emboli are arrested by the first capillary or arteriolar bed, but some emboli may immediately pass through the capillaries and be carried to other regions. The pattern of distribution of metastases depends in part on mechanical factors and, in part, on recently recognized effects...
of hormones, notably of the adrenal. These hor-
mones act on the tumor embolus or on the tissue
where it has lodged.

Studies on the lymphatic spread of cancer re-
veal that tumor cell emboli of carcinomas are ar-
rested in the subcapsular sinus of one or more
lobules of the lymph node, and it is here that early
growth occurs. The cancer is contained by the
node for some time before spread to the next node
occurs. While growing in a node, the cancer has no
supply of lymphatic vessels. When tumor emboli
reach the thoracic duct, some of them may go
directly to nearby lymph nodes without first
go through the lungs.

REFERENCES

1. AAGEN, M.; CHRISTEN, R.; BADNICK, O.; GARIC, G.; NI-
BIRKH, A.; PIARRO, O.; and JARPA, A. Cortisone-in-

2. AMBUST, J. L.; AMBUST, L. M.; BYRON, J. W.; GOLDBERG,
J. E.; and HARRISON, J. W. E. Study of Metastasis with

3. BANBERG, R., and SHUBIK, P. The Action of Cortisone on
Transplanted and Induced Tumors in Mice. Cancer Res.
14:12–14, 1954.

4. Action of Cortisone on Disseminated Tumor Cells
after Removal of the Primary Growth. Science, 121:100–

5. BANBERG, R., and SAPPITTO, U. Experimental Studies on
Histogenesis of Blood-borne Metastases. Arch. Path., 69:

6. RATON, O. V. The Function of the Vertebral Veins and
Their Role in the Spread of Metastases. Ann. Surg., 113:
130–49, 1940.

7. ——. The Role of the Vertebral Veins in Metastatic

8. BEEBE, S. P. The Chemistry of Malignant Growths. II.
The Inorganic Ion Constituents of Tumors. Am. J.

9. BRUNSHWIG, A.; DUNHAM, L. J.; and NICHOLS, S. Potas-
sium and Calcium Content of Mouse Tumors (Adeno-

10. CAHRUTHERS, C., and SUNTZEFF, V. Calcium, Copper, and
Zinc in the Epidermal Carcinogenesis of Mouse and Man.

11. AMBRUB, J. L.; AMBRUS, L. M.; BYKON, J. W.; GOLDBERG,
M. E.; and HARRISON, J. W. E. Study of Metastasis with

12. COMAN, D. R., and ANDERSON, T. F. A Structural Differ-
ence between the Surfaces of Normal and of Carcinoma-

13. COMAN, D. R., and DELONG, R. P. The Role of the
Vertebral Venous System in the Metastasis of Cancer to

14. COMAN, D. R.; DELONG, R. P.; and MCCUTCHEON, M. Studies on the Mechanisms of Metastasis. The Distribu-
tion of Tumors in Various Organs in Relation to the Dis-

15. DELONG, R. P.; COMAN, D. R.; and ZEIDMAN, I. The Sig-
nificance of Low Calcium and High Potassium Content in

16. DUNHAM, L. J.; NICHOLS, S.; and BRUNSHWIG, A.


18. GILCHRIST, R. K. Surgical Management of Advanced

19. GILDE, H.; WALKER, M.; JEFFRIES, B. R.; and GUT, R.
Pattern of Tumor Cell Spread in Tissues and Organs as a
Lethal Factor in Tumor-bearing Animals. Cancer Research,

20. GOLDMAN, E. E. Studien zur Biologie der bösartigen

21. GREEN, H. N. S. The Significance of the Heterologous
Transplantability of Human Cancer. Cancer, 5:24–44,
1952.

584. 2d ed. Philadelphia & London: W. B. Saunders Co.,
1948.

23. HUSEBORN, K. A.; LARRSON, L. G.; and RAGNEKUZ, I.
The Lymph Drainage from the Breast to the Axillary and
Parasternal Lymph Nodes Studied with the Aid of Col-

24. IWASAKI, T. Histological and Experimental Observa-
tions on the Destruction of Tumor Cells in Blood Vessels.

25. KADISH, N.; BORGES, P. R. F.; and DAY, E. D. The Sur-
vival of Homografts of Mouse Tumors in Mice Pretreated
with Lyophilized Tissue and Cortisone. Cancer Research,

26. KAZUWA, K. Unpublished data quoted by HAUSCHKA,
T. S.; KURDAR, K. J.; GRINNELL, S. T.; and AMOS, B. D.
Immunoselection of Polyploids From Predominantly
1956.

27. KOLLER, P. C. Cytological Variability in Human Car-

28. KORPÁSSY, B.; KOVÁCS, K.; and TIBOLDI, T. Transplenic

29. KAZIWARA, K. Unpublished data quoted by HAUSCHKA,
T. S.; KURDAR, K. J.; GRINNELL, S. T.; and AMOS, B. D.
Immunoselection of Polyploids From Predominantly
1956.

30. KAZIWARA, K. Unpublished data quoted by HAUSCHKA,
T. S.; KURDAR, K. J.; GRINNELL, S. T.; and AMOS, B. D.
Immunoselection of Polyploids From Predominantly
1956.

31. KOLLER, P. C. Cytological Variability in Human Car-

32. KORPÁSSY, B.; KOVÁCS, K.; and TIBOLDI, T. Transplenic

33. LEUCHTENBERGER, C.; LEUCHTENBERGER, R.; and
DAVIES, A. M. A Microspectrophotometric Study of the
Passage of Tumor Cell Emboli. Acta Morphologica,

34. LEUCHTENBERGER, C.; LEUCHTENBERGER, R.; and
DAVIES, A. M. A Microspectrophotometric Study of the
Desoxyribose Nucleic Acid (DNA) Content in Cells of
Normal and Malignant Human Tissues. Am. J. Path., 30:

35. McCUTCHEON, M.; COMAN, D. R.; and MOORE, F. B.
Studies on Invasiveness of Cancer. Adhesiveness of


54. ———. Experimental Studies on the Spread of Cancer in the Lymphatic System. I. Effectiveness of the Lymph Node as a Barrier to the Passage of Embolic Tumor Cells. Ibid., 14:405-5, 1954.


Metastasis: A Review of Recent Advances

Irving Zeidman


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/17/3/157

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.