Two distinguishing biological characteristics of malignant tumors are their ability to invade adjacent normal tissues and their ability to produce secondary tumors in distant parts of the body. Local tissue invasion is a prerequisite to the formation of blood-borne metastases, for thus the tumor cells gain entrance to the vascular system. Therefore, an understanding of the mechanisms of metastasis begins with inquiry into the phenomenon of invasiveness. It is the purpose of this review to re-examine our concepts concerning these two features of neoplasia in the light of knowledge gained from experiments during the past ten or more years. The need for such a review is evident from the usual textbook treatment of the subject; the concepts presented therein are essentially those advanced by the earlier pathologists as a result of their interpretations of autopsy material. This has become misleading, for there has accumulated an important body of knowledge, derived from carefully conducted experiments, that adds considerably to our understanding of these fundamental processes. The present review is not intended as an exhaustive treatise including every experimental approach to these problems; rather, it is an attempt to sift out what appears, at this time, to be most pertinent and to arrive at tentative concepts that seem to account for the major part of the observed events.

**MECHANISMS OF INVASIVENESS**

By invasiveness is meant the ability of cells to penetrate the tissues surrounding them. Invasiveness is not restricted to the cells of malignant tumors. Some of the normal cells of the body—leukocytes and macrophages, for example—invasive other tissues as readily as do cancer cells. Thus, the capacity to permeate other tissues is a quality peculiar to certain cells, normal or malignant. Cells of malignant tumors derived from noninvasive normal cells, therefore, must have some biological attribute not shared by the cells of benign tumors or by most normal cells, but present in leukocytes and macrophages. As Willis said, "...the invasive properties of tumors reside largely or entirely in the tumor cells themselves" (53).

Such factors as multiplication rate, liberation of lytic substances, and loss of growth restraints can no longer be regarded as essential factors in invasiveness, since these qualities either are shared by noninvasive tumors or do not exist in malignant tumors.

The invasive properties of leukocytes and macrophages depend on their being isolated single cells and on their highly developed ameboid motility. That cancer cells also possess ameboid motility was reported as long ago as 1863 by Virchow (48) and has been demonstrated in tissue culture by many workers in recent times (8, 11, 18, 23, 26, 31, 33, 35, 43). These tissue culture studies have shown beyond all doubt that tumor cells in general are ameboid, whether they are of mesodermal or epithelial origin.

Neoplastic epithelial cells from carcinomas of man and of laboratory animals have been photographed with a moving picture camera and their rates of speed determined (23). Cells from breast cancers, for example, moved at an average of 0.7 μ/m/min, with a maximum rate of 2.4 μ/m/min. Cells from a carcinoma of the kidney attained...
a maximum rate of 4.4 μ/min, while some cells from a mouse fibrosarcoma traveled at 6.2 μ/min. Of additional interest is the observation that even tiny clusters of from three to five epithelial cells from a rabbit carcinoma progressed as an ameboid unit. It was also demonstrated that the cells of benign epithelial tumors and even non-neoplastic glandular epithelial cells (from cystic disease of the breast) may be motile in tissue culture, provided that these cells are first forcibly detached from their companion cells. It appears probable, then, that the local invasiveness of cancer cells depends upon their ability to progress by ameboid movement.

Why, then, do not the cells of benign tumors or the cellular components of the various organs also invade, since they too, at least in some instances, are capable of ameboid motility? There is evidence to indicate that the cells of normal tissues and also the cells of benign tumors are so firmly attached to one another that they are unable to escape. In contrast, the cells of malignant tumors are often found in the body free from the parent tumor.

The reason that the cancer cells become free is their greatly reduced adhesiveness. Micromanipulation studies (12) have shown that the magnitude of force required to separate a pair of normal squamous epithelial cells from each other is much greater than the force required to separate cancerous squamous cells. Also, the individual cells from various malignant adenocarcinomas from man were found to be easily dislodged by a mechanical shaking of the cancerous tissue, whereas shaking the normal prototype tissue dislodged few or no cells (37).

The deficiency in the adhesiveness of cancer cells, then, permits them to separate easily from their mutual attachments. Once free, they are capable of ameboid motility. The lowered adhesiveness of cancer cells has been related to a deficiency in calcium (12, 20). Recognition of the role played by calcium in maintaining the adhesiveness of normal cells dates back to the observations of Herbst (27) on the blastomeres of sea-urchin eggs. When placed in a calcium-free medium, the individual blastomeres become separated, losing their ability to cling to each other. Calcium deficiency in cancerous tissues has been reported by several independent investigators (4, 7, 10, 20, 21). For example, the calcium content of a group of human cancers has been found, by flame spectrophotometric determinations, to be about 40 per cent less than that of the normal prototype tissues. That the loss of calcium in the cells is dependent upon their neoplastic character, rather than upon the fact that such cells are rapidly multiplying, is emphasized by observations made upon regenerating rat livers. In this material, although the cells were actively proliferating, there was no demonstrable decrease in calcium (20). Hepatomas of rats, on the other hand, are deficient in calcium (25). Moreover, procedures designed to decrease the calcium content of normal cells have resulted in reducing their adhesiveness. It was shown, by Carruthers and Suntzeff, that methylcholanthrene, when applied to mouse skin, causes a reduction in the calcium (9, 47), and, by Zeidman, that this same substance causes a loss of adhesiveness when applied to normal squamous cells (55).

The possibility that cancers liberate hyaluronidase and that this enzyme, by hydrolyzing the hyaluronic acid of connective tissues, opens pathways for the invading cancer cells has been explored (5, 6, 16, 22, 36). That hyaluronidase may somewhat increase the invasiveness of tumors that are invasive to start with has been reported by Simpson (45). When cancers do contain hyaluronidase, the enzyme may possibly facilitate invasion of the surrounding normal tissues, but that it is a requisite to, or even a frequent factor in, invasiveness appears doubtful.

From the combined evidence it seems safe to conclude that the invasiveness of cancer cells depends largely upon a loss of adhesiveness that is associated with, if not due to, local calcium deficiency. Most cell physiologists agree that calcium is located principally at the cell surface, but how it is combined there and why the cancer cell is unable to bind the normal amount of calcium is as yet unknown. Reduced adhesiveness, however, is what permits the cells to become free-living, detached units that thereafter progress by their own ameboid motility.

THE RELATION OF INVASIVENESS TO METASTASIS

As described earlier, it is characteristic of cancer cells to separate from one another and then to travel by ameboid motion through the tissues. In their course of travel they follow paths of least resistance. They penetrate loose tissue such as muscle or areolar tissue more readily than hard and compact tissue such as bone and cartilage, the latter often remaining long intact. Cancers of the prostate, for example, infiltrate the loose tissues of the nerve sheaths in preference to the dense parts of the gland itself (29, 38, 52). The lymphatics offer natural preformed paths of low resistance. Along these avenues cancer cells may grow as solid cords or be carried along in the current. Similarly, cancer cells in general have little difficulty in penetrating
stroma.—Are there differences in the ability of cells as capable of survival in one part as in another organs, and in what parts of the vascular system upon the following fundamental processes: normal tissues to furnish the lodged tumor cells affect their survival, favorably or adversely? Other, or do peculiarities in the local environment within the organs, are the tumor cells arrested, and distribution of metastatic tumors?

The answers to these questions depend in turn upon the following fundamental processes:

1. **Lodgement of the embolic tumor cells.**—In what organs, and in what parts of the vascular system within the organs, are the tumor cells arrested, and does this differ from organ to organ?

2. **Survival of the arrested embolic cells.**—Are the cells as capable of survival in one part as in another, or do peculiarities in the local environment affect their survival, favorably or adversely?

3. **Establishment of a new blood supply and stroma.**—Are there differences in the ability of normal tissues to furnish the lodged tumor cells with supporting connective tissue and blood vessels?

4. **Growth of the tumor.**—Are there local environmental conditions in different parts of the body that affect, favorably or adversely, the rate of multiplication of the tumor cells?

**Factors Affecting the Number of Metastatic Tumors**

What factors determine the number of metastases produced by a primary tumor?

As might be expected, the number of embolic cells is an important factor. This was demonstrated by injecting different numbers of cells of a transplantable sarcoma into the tail vein, in mice, and counting the number of resulting tumors in the lungs. A direct proportionality was found between the number of living embolic cells and the number of tumors (57).

The mortality of embolic cells is very high. Warren and Gates (51) studied the fate of tumor cells introduced into the systemic veins of the mouse. Only a small percentage survived. The enormous majority of embolic cells fail to establish themselves in the lungs and to form tumors (28, 57). These findings confirm the conclusions drawn from study of autopsy specimens (44, 53, pp. 175, 179).

Since, as stated above, the number of tumors is proportional to the number of embolic cells, the original question concerning the number of metastases produced by a primary growth may be re-stated as follows: What factors in the primary tumor affect the number of tumor cell emboli released into the circulation?

**The age of the primary tumor.**—With the use of a transplantable tumor in inbred mice, the number of metastases was found to be proportional to the duration of growth of the primary tumor (57). Animals were sacrificed at different times after tumor implantation, and metastatic lung tumors increased in numbers with the age of the primary growth. That is, the longer the tumor existed, the greater were the number of metastases.

**The size of the primary tumor.**—It is a well established fact that the size of the primary tumor in man is no criterion of the number of metastatic tumors. In man, it should be emphasized, both host and tumor constitute uncontrollable variables. However, under experimental conditions, these factors can be controlled. In inbred strains of mice, the identical tumor may be implanted in almost identical hosts. Under these conditions, it might be expected that the size of the primary tumor would have an appreciable effect on the number of metastases, since the number of potential embolic cells would be greater in large tumors than in small ones.

When mice were inoculated with fragments of a transplantable tumor, those that received larger
implants developed more metastases than those receiving smaller ones (57). However, when the final sizes of implanted tumors were compared to the number of metastases, no correlation was found, as the number of metastases varied so greatly from one animal to another. This result is consistent with what is found in man: the number of metastases is not apparently related to the final size of the primary tumor. In the study just cited, the wide scatter in the number of secondary tumors, even under these controlled conditions, indicates the existence of factors as yet unknown that influence the number of metastases far more effectively than does the element of size.

Factors Affecting the Distribution of Metastatic Tumors

The distribution of metastatic tumors is a problem that has fascinated pathologists and clinicians for many years, but this problem has been starred at rather than investigated. Why are some organs frequently the site of secondary tumors, while others are rarely so? Why do some tumors metastasize frequently to one organ and only rarely to another? By what pathways do tumor cells travel from a primary growth to some remote portion of the body?

It was in an attempt to answer these questions that Paget (39) likened embolic cancer cells to seeds scattered in soils of different degrees of fertility, to grow only where the soil was suitable. This "soil" hypothesis was based upon the supposition that local chemical factors rendered some parts of the body (e.g., muscle and spleen) relatively unsuitable for the development of secondary tumors, while in other organs (e.g., bone marrow and liver) conditions were specifically favorable for the survival and multiplication of embolic tumor cells. The "soil" hypothesis has found wide acceptance.

An alternative hypothesis, a mechanical explanation, was proposed by James Ewing, who stated: "The mechanics of the circulation will doubtless explain most of these peculiarities, for there is as yet no evidence that any one parenchymatous organ is more adapted than others to the growth of embolic tumor cells" (24). This sentence was deleted from the final edition of Dr. Ewing's book, suggesting that he became less certain of its tenability.

Metastasis through Venous Channels

The three commonest sites of metastatic tumors in man are the lung, the liver, and the bones of the axis and trunk (1, 17, 30, 92, 42, 49, 53, p. 178, 54). That the lungs and liver should be so frequently involved is readily understandable, since the lung receives the venous drainage from the cava system, and the liver the portal drainage. But why the bones of the axis and trunk? The "soil" hypothesis would account for the frequency of secondary tumors in the bones generally by attributing to them peculiarly favorable conditions for tumor development. Presumably, according to this concept, the pelvic bones and shoulder girdle are better "soil" than are the tibia and radius! However, an alternative explanation is available.

Oscar Batson (2, 3) suggested that tumor cell emboli from the prostate might enter the vertebral venous system and be carried directly to the bones of the spine, pelvis, and skull, by-passing the lungs entirely. He showed that increase in intra-abdominal pressure, such as would result from coughing or straining, would facilitate the passage of embolic cells into the vertebral veins by diverting the flow of blood from the caval system into the vertebral veins. Recently, it has been shown by experiment (13) that this pathway is indeed used. Suspensions of tumor cells injected into the femoral veins of rats and rabbits, while the abdominal pressure was slightly elevated, were diverted into the vertebral veins and produced tumors in the vertebrae. Tumor cell emboli were found plugging the ramifications of the vertebral veins.

Since the vertebral veins form an extensive system from the pelvis to the skull, anastomosing freely with the caval system at each segmental level, yet not subject to pressure changes within the body cavities, it is not surprising that embolic cells readily enter these vessels and lodge in the spine, skull, and pelvis. The mammary veins, for example, communicate with the vertebral system through the intercostal and subclavian veins; hence it is understandable that in man breast cancer should metastasize frequently to the spine and pelvis. The thyroid occupies a position in the neck as favorable for this route as that of the prostate in the pelvis. Indeed, since the vertebral and systemic veins communicate at each segmental level, it is not surprising that tumors in almost any location may sometimes metastasize to the axial bones.

It would appear, then, that the three most common foci for metastatic tumors—the lungs, the liver, and the bones of the skeletal axis—are situated as one would expect them to be, on the basis of the anatomical arrangement of the veins of the body.

Metastasis through Arterial Channels

Less commonly, metastatic growths appear in other areas, such as the kidneys, adrenals, spleen, and muscle, emboli having reached these organs.
through arteries. In these instances the embolic tumor cells must have gained entrance to the arterial side of the circulation by filtering through the vascular bed of the lungs (this possibility will be discussed later), or by secondary metastasis from pulmonary foci (50). Also, the liver and lungs may receive emboli through arteries (the hepatic and bronchial, respectively) instead of through the veins, as is more frequent. The bones, too, may receive emboli through the arterial circulation (50). This is true not only of the bones of the axis and trunk but of all the bones in the body.

Having entered the arterial blood stream, the cells may be carried anywhere. Why, then, of those organs receiving their emboli exclusively by the arterial circulation, are some more frequently the site of metastases (kidney and adrenal) than others (muscle and spleen)?

Recent work designed to answer these particular questions will now be described in some detail.

By good fortune there is available a transplantable tumor of rabbits, the $V_1$ carcinoma, that has the property of spontaneously metastasizing to the lungs and regional lymph nodes but, except in rare instances, to no other organ. Here, to all appearances, is a tumor the behavior of which conforms to the "soil" rather than the mechanical hypothesis. From the mechanical standpoint, the explanation for this behavior is that tumor emboli in adequate numbers rarely reach organs other than lungs and regional lymph nodes, whereas, if they could be made to reach other organs, tumors would appear there.

This prediction has been verified by experiment. Cell suspensions of the $V_1$ carcinoma were injected into the left side of the heart, which meant that, necessarily, emboli would be carried to every organ of the body. Accordingly, tumors appeared and grew in virtually every organ (15). Thus, it became evident that the $V_1$ carcinoma fails to metastasize widely, not because the various organs offer an unfavorable chemical environment but because adequate numbers of tumor cells do not reach those organs.

Still left entirely unexplained, however, was the fact that metastatic tumors were far more numerous in some organs than in others—as, of course, is true in spontaneous metastases of every kind of tumor. Thus, in the experiments just cited, tumors were numerous in kidneys, eyes, adrenals, but infrequent in spleen, muscles, and thyroid. The mechanical hypothesis had to account for these differences if it were not to be invalidated.

The "soil" concept would explain the unequal distribution of the $V_1$ carcinoma as owing to (a), the inability of all but a few tumor emboli to establish a blood supply in such unfavorable soil as muscle and spleen or (b) the fact that, even if some emboli survived in these organs, metastatic tumors would grow very slowly because of unfavorable chemical conditions and might not even attain macroscopic dimensions.

These explanations, deduced from the "soil" hypothesis, were tested in rabbits, rats, and mice with four different kinds of tumors (19). Fragments of these tumors were implanted into muscle, spleen, liver, kidney, and adrenal. There was no difference in the number of "takes" in the several organs; there was no observable difference in the rate of growth, except that one type of rabbit tumor grew slightly faster in the spleen than in the other organs tested. Therefore, these experiments did not support the view that tumors acquire a blood supply more easily, and subsequently grow better, in some organs than in others.

Another explanation for differences in organ-distribution of tumors was then tested (14). According to this explanation, the reason that greater numbers of secondary tumors are found in the kidney and adrenals than in the spleen, muscles, and thyroid is that greater numbers of tumor emboli reach the kidney and adrenal than the other organs; the number of tumors in each organ was predicted to be proportional to the number of emboli that reach it.

To ascertain the relative number of tumor emboli reaching the several organs, cells of the Brown-Pearce rabbit tumor were fixed and stained, to facilitate recognition, and then injected into the left side of the heart. Animals were sacrificed at once, histological sections were prepared, and the emboli in arterioles and capillaries were counted, and computed as emboli per square centimeter, for each of the eight organs. Living tumor cells were similarly injected, in another series of animals, which were allowed to survive until the tumors had time to grow. Then the tumors were counted in histologic sections.

When the total number of stained cells reaching an organ was compared to the number of tumors in that organ, correspondence was only fair. However, if only those embolic cells that lodged in the capillaries were considered, correspondence was excellent. Thus, the greatest number of emboli per square centimeter was found in iris, pituitary, adrenals, and kidneys; the smallest number in muscle, thyroid, and spleen. The same frequency distribution was found for the tumors.

It was further demonstrated that the anatomical frequency distribution of the naturally occurring metastases of this tumor was predictable on the basis of the distribution of the embolic stained...
cells; that is, the agreement between the lodgement of stained cells was almost exactly parallel with the order of frequency reported by Pearce and Brown (40) as characteristic of the organs to which their tumor metastasized.

This seems to afford fairly conclusive evidence that the anatomical distribution of metastases, of this tumor at least, is chiefly dependent upon the frequency distribution of embolic tumor cells.

It has been noted in examinations of autopsy specimens that embolic tumor cells lodging in arterioles frequently do not survive, in contrast to those that lodge in capillaries and thin-walled veins (53, p. 178). This observation is also confirmed by the experiment described above, wherein injected cell suspensions produced tumors in those instances only where the cells lodged in capillaries and sinusoids. The spleen, for example, received relatively few embolic cells, and those it did receive lodged chiefly in the tiny, thick-walled arterioles; tumors did not result. This was in contrast to the kidney, where large numbers of embolic cells were arrested, chiefly in the glomerular loops in which location numerous tumors resulted.

Correlated with these observations is the finding that single tumor cells, or clusters tiny enough to penetrate the capillaries, were more successful in producing tumors than were large clumps, because the latter were arrested in arterioles. This is contrary to some reports based upon autopsy material (53, pp. 175, 179).

That the distribution of metastases may vary for different tumors, even though the site of origin of their embolic cells is the same, has been indicated in our own studies (14, 15) as well as by Sugarbaker (46). These observations emphasize only that all tumors are not identical in their behavior. Until we find ways to test critically their subtle peculiarities, we can only speculate as to the reasons for their vagaries.

PROBLEMS IN METASTASIS PECULIAR TO THE LUNGS

There are two points of interest peculiar to the lungs:

1. The problem of transpulmonary passage of embolic tumor cells.—It has been suggested (52) that, except for tiny tumor cells, such as lymphoblasts, tumor cells are for the most part arrested in the lung capillaries. If so, secondary growths in other organs that receive emboli through the arteries would depend upon the release of cells from metastatic tumors that have become established in the lungs. However, Prinzmetal et al. have recently shown (41) that glass beads having a diameter much greater than that of ordinary capillaries are capable of passing readily through the pulmonary circulation. This observation suggests the existence of arteriovenous shunts in the lungs sufficiently large to allow almost any tumor cell to pass through. In confirmation of this, it has been shown that tumor cells considerably larger than lymphoblasts do indeed immediately pass through the lungs. Zeidman (56) found that suspended tumor cells injected into the systemic veins of one animal could be recovered immediately from the aortic blood, and, when injected into a second animal, produced tumors. Three different tumors in two species (rabbits and rats) were used in this study, and in each the cells passed immediately through the lungs. It seems probable, then, that the transpulmonary passage of embolic tumor cells is a more common occurrence than previously supposed.

2. The lung as a site of growth.—That the lung may differ from some other organs in its ability to support the growth of metastatic tumors has been demonstrated recently by Lucké et al. Tumor cell suspensions introduced into the hepatic and pulmonary circulation produced larger tumors in the liver than in the lungs, and, although more tumors appeared in the lungs, their total mass was less than that of the hepatic tumors (34).

Also, in studies on autopsy material (53, pp. 175, 179), necrotic and degenerating tumor emboli are far more commonly seen in the lung than in the liver.

If any organ does differ from the others in ability to support the growth of secondary tumors, it might, on theoretical grounds, be predicted that the lung would be that organ. The lung is essentially an air-filled sponge, in contrast to the solid structure of other organs; it is continually expanding and contracting, and it is continually subjected to physiological changes in pressure. These factors must in turn affect the circulation of the organ. It is reasonable to suppose that such physical, mechanical, and circulatory events would have some effect upon the establishment of secondary tumors.

Thus, from the evidence at hand, one would conclude that conditions for tumor growth are relatively unfavorable in the lung.

It would seem, at first, paradoxical that the most frequent site of all metastatic tumors, the lungs, should provide the least favorable conditions for the event to occur. This paradox is dissipated when the fact is taken into account that the lung receives the entire systemic venous drainage
and, hence, must be the site of arrest of many more emboli than reach other organs. If only a few of these emboli survived, it would be expected that the lung would still be the organ most commonly the site of metastases.

**SUMMARY**

Combining the results of the investigations reviewed in this paper, the following concepts relative to the dissemination of malignant tumors within the body are tentatively advanced:

The local invasiveness of cancer cells is primarily dependent upon loss of the mutual adhesiveness of the cells, which loss is associated with, if not due to, local calcium deficiency. The easily detached single cancer cells, or even small clusters of them, are actively ameboid and are thereby enabled to penetrate the adjacent normal tissues.

Distant dissemination of cancer cells, as a sequel to local invasiveness, is largely dependent upon entrance of cells into vascular channels through which they are carried to other parts of the body. Many embolic cells, however, are unable to establish secondary growths in their new location.

Duration of growth of the primary tumor bears a positive relationship to the number of metastases, whereas the size of the primary tumor is less effective in influencing the number of metastases than are other factors as yet undetermined.

The venous distribution of metastases is largely dependent upon the anatomical arrangement of the venous channels (including the vertebral veins) into which emboli are commonly released. This accounts for the frequency of metastatic involvement of the lungs, the liver, and the bones of the spine, pelvis, and skull.

The arterial distribution of metastases is also dependent upon the number of embolic cells reaching the various organs, and in addition depends upon whether the embolic cancer cells lodge in capillaries and sinusoids or in thick-walled arterioles. These phenomena are variable from organ to organ, and evidently account in large measure for the relative infrequency of metastasis to some organs (spleen, muscle) and the frequency of metastasis to other organs (adrenals, kidney).

The lungs, however, although frequently the site of metastatic tumors, apparently afford relatively adverse conditions for tumor growth. This may be attributable to the peculiar physical structure, functions, and circulatory mechanisms of the lungs. The immediate transpulmonary passage of embolic tumor cells is perhaps more common than has been thought in the past.

It is further indicated that single embolic cells or tiny clusters, rather than large clumps, give rise to most metastases because these cells are able to reach the capillary bed where conditions are most favorable for the development of secondary tumors. Larger clumps lodge in arterioles, a situation unfavorable for the establishment of metastatic growths.

In the attempts herein reviewed to reveal "soil" factors as affecting the distribution of metastases, it would appear that they consist chiefly of physical or mechanical circulatory differences rather than of chemically favorable or unfavorable environments for the growth of tumor cells. In view of the results obtained in the experiments here reviewed, it is suggested that before hypothetical "chemical soil" factors are offered in explanation of the distribution of metastatic tumors, simple "mechanical-circulatory" factors affecting the frequency distribution of embolic tumor cells must be eliminated for each tumor and host studied.

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Mechanisms Responsible for the Origin and Distribution of Blood-borne Tumor Metastases: A Review

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