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Cancer Permeation: Processes, Problems, and Prospects—A Review

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SUMMARY

Permeation is the scientific term introduced in 1905 by Handley to signify the spread of cancer cells in continuous columns within the lymph vessels. The phenomenon itself was known to workers of much earlier times and, to date, its processes largely have been documented. However, some problems have arisen. There is, for example, considerable confusion because different authorities have classified it under both direct and metastatic spread. Evidence is therefore adduced from the literature to show that the columns of cancer cells seen in permeation are not absolutely continuous but partially continuous. It is this element of discontinuity that confers on permeation the status of a metastatic phenomenon. If this status is recognized, a continuing source of confusion will disappear from the literature and new prospects will open in this important facet of oncology.

INTRODUCTION

In a lecture aimed at furthering medical research, Gregg (26) spoke of the need to pay due attention to the *meaning* and *use* of words. Accordingly, I propose here to attend to both of these recommendations, concentrating on an important term in oncology, namely, *permeation.* Although the processes manifested by lymphatic permeation may be common knowledge, there are some word-dependent problems that are discernible in its literature. The probability is that, if these problems are defined and resolved, brighter prospects will dawn in research on cancer dissemination.

PROCESSES

Definition. Moore's (43) definition is typical: "By 'lymphatic permeation' is meant formation within a lymph vessel of a continuous column of neoplastic cells from the primary tumor to the secondary nodules." Or, as Yoffey and Courtice (73) stated, "Columns of invading cells may be seen occupying distended lymphatics whose endothelial walls are still intact."

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Description. Permeation has been described simply in terms of "columns" (5), but it is more usual to apply a qualification, *e.g.*, "solid columns" (17) and "uninterrupted columns" (42). Other picturesque descriptions are "lines" (34, 52) and "strands" (37, 71). Perhaps the most commonly used descriptive word is "cords" (3, 12, 16, 54, 56).

History. It is only natural that such bold cords of tumor tissue would attract the attention of the old masters. As long ago as 1841, Walshe (65) made the distinction that the lymph vessels connecting a tumor to an invaded lymph node are either "in the natural state" or "loaded with cancerous substance." A decade later, Paget (51) also distinguished between those cases "in which lymphatics, filled with cancer, have been traced from the primary growth to the nearest glands" and the other cases in which "such tracts of cancer cannot be traced from the primary disease to that in the lymphatic glands."

Subsequently, authorities like Macewen (40) in Scotland and Woodward (72) in the United States wrote in plain terms about the existence of lymph vessels lined throughout by invasive cancer cells; so did their contemporaries (22, 24, 30, 31).

In 1874, de Morgan (19) described the local spread of breast cancer in a prophetic manner: "The disease will seem to prefer the easier course, but the densest tissues will not prevent this *permeation.*" My *italics* draw attention to his apt use of the word which was used much later in 1905 by Handley (28, 29) to usher in an enduring theory of cancer dissemination. So rapidly received was his permeation theory that by 1906 Bland-Sutton (9) had cited it approvingly.

Pathology. Let us summarize the consensus on the pathology of permeation.

1. Its appearance is usually contrasted with that of embolism (10, 13, 44, 60). Crawford (17) was explicit: "Two modes of lymphatic spread are recognized: *lymphatic embolism*, when fragments of tumour are transported in the lymph stream . . . and *lymphatic permeation*, in which the tumour cells grow as solid columns . . . ."

2. Its incidence is comparatively less than that of embolism (10, 58, 64, 70). Both Fried (23) and Warren (67) stated that permeation occurs "in rare instances."

3. Its prominence is noted in the later stages of spread (41, 63, 64).

4. Its prevalence is evident in the vicinity of the primary growth (34, 68, 71). It may also be impressive in more distant destinations (15, 59, 69, 74).

5. Its preponderance is recorded in certain tumors (55, 63, 71) and in particular areas such as the pelvic organs (4, 39) and serous membranes (6, 12, 41, 52).

6. Its performance is acclaimed with respect to the invasion of lymph nodes (2, 10, 42, 70). On the contrary, there is cautious acceptance with regard to the invasion of named organs such as the adrenal (33, 59), kidney (53, 70), liver (32, 61), lung (14, 41), and spleen (25). Rarely, it has been admitted as the major mode of spread to an organ, *e.g.*, heart (36).

7. Its presence is demonstrated in vessels of small caliber most commonly, but there may also be extension to the larger trunks (17, 52), including the thoracic duct (70, 74).

8. Its occurrence is apparent in the normal direction of lymph flow, but spread in the retrograde direction may occur (6, 14, 36, 44).

PROBLEMS

An outstanding problem, recognized by Karsner (34), is the existence of 2 schools of thought on the classification of permeation. One school classifies it under direct spread (42, 66, 73); Willis (71) restricted its discussion to a subheading in his chapter on the direct spread of tumors. The other school favors its inclusion under metastatic spread (7, 11, 43); Warren (67) discussed it under the subheading on metastasis in his chapter on neoplasms.

A debated problem is the possibility of lymphogenous spread to structures other than lymph nodes. When weighing the merits of the lymphatics as a possible pathway for extranodal invasion, one tends to restrict the field of evidence to the presence of *permeated* vessels, thus neglecting the possible role of *embolized* vessels. In other words, as far as extranodal sites are concerned, there is a tendency to equate lymphatic invasion with permeation. If permeation lines do not lead right up to the extranodal site being considered, then it is argued that transportation to it has probably not been lymphogenous. For example, there is the view of Pack and Brasfield (50): "Extension of cancer to the liver via the lymphatics is probably uncommon; one seldom sees lymph vessels permeated by cancer except in the immediate vicinity of massive metastases." Much the same argument was used by Willis (70) when he dismissed the significance of lymphatic spread to this organ: "it is unusual to see cancerous lymphatics in the portal tracts, save in the immediate neighbourhood of masses of growth."

Finally, there is the disputed problem of the degree of importance attachable to permeation. Divergent views exist. On one hand, as Cowdry (16) stated it: "Neither is spread by permeation of great statistical significance." On the other hand, Berenblum (7) had "no doubt that it does play a significant role."

PROSPECTS

What are the future prospects in this field? Perhaps a brighter era will dawn with the resolution of the crucial question of the rightful status of permeation. Is lymphatic permeation classifiable as direct spread or as metastatic spread?

Admittedly, we started this review with the definition of permeation as a "continuous" process, and we know that the "cardinal feature" (21) of metastasis lies not in its being a "continuous" but a "discontinuous" (62, 68, 70) process. However, it is necessary to emphasize that there are 3 cogent arguments for modifying the old simplistic definition of permeation.

First, even from Handley's original work, it was already plain that permeation does not proceed in *absolute* continuity. This was why attempts were made to bring in the concept of "perilymphatic fibrosis" (20, 29) to explain away the embarrassing breaks noted along permeation lines. What is fundamental is that, in the vicinity of a tumor, the spreading cells do not merely lie in "columns" but in "incomplete columns" (8).

Secondly, it is generally accepted that *fusion* of initially discontinuous deposits is part and parcel of permeation (1, 27, 35, 67). Willis (70) argued persuasively, "It must not be assumed, however, that extensive lymphatic permeation always proceeds centrifugally from a single focus. Frequently several or many focal deposits of growth participate, the initially separate permeation zones around these become confluent and so establish a wide permeated area which, though now continuous, was of multicentric origin."

Thirdly, there is *nodularity* even in permeation. Moore (43) wrote, "Permeation is acceptable as an explanation of the small satellite nodules in the mucosa about carcinomas of the stomach or of the bronchus and of the multiple epidermoid carcinomas of the skin in a localized region in some patients." Willis (71) gave examples of permeation with "outcrop-nodules" in the skin and with "fine nodular branching strands" in the lung. In the latter site, there are other apposite descriptions of such permeated networks, *e.g.*, "nodules . . . arranged like a string of beads" (18) and "fine strands spreading between the nodules" (37). These are all descriptions of a process with an underlying unevenness and poor continuity.

The above observations lead to the conclusion that there is an element of discontinuity in permeation. This is what confers on the process the status of a metastatic phenomenon. It is by virtue of its formation through *partial* continuity that permeation differs from direct spread, which displays *perpetual* continuity.

Accordingly, the following definition is recommended. *Permeation is the formation of partially continuous columns of invading cancer cells within the lumen of a vessel.* If this definition is accepted, the conflicting interpretations given to permeation will disappear from the literature, ending a potent impediment to the understanding of secondary tumors. Clearly, unless permeation is accepted by every writer as a mode of metastasis, albeit one that may closely mimic direct spread, the literature will continue to harbor contradictory statements, *e.g.*, "most" pericardial secondaries being claimed

to be metastatic by one group of workers (38) but nonmetastatic by another group (57).

If permeated lymphatics are seen coursing into a viscus, their presence denotes that *one* of the modes of lymphatic metastasis has been effective in conveying cancer cells to that viscus. In this way, the phenomenon of permeation assists us by providing a recognizable hallmark of lymph-borne visceral invasion.

No such assistance is afforded us by the *other* mode of lymphatic metastasis. Alas, embolism has no emblem. We are left, therefore, with the unassisted task of recognizing those visceral deposits which are both lymph borne and embolic. Elsewhere (45–49), I have suggested some methods for circumventing this difficulty. Here, let me draw an analogy. Since pure lymphatic permeation is less common than lymphatic embolism, those visceral deposits due to the readily discernible metastasis of the pure permeation variety must be less common than the remaining visceral deposits due to the poorly discernible metastasis of the embolic variety. Accordingly, the totality of visceral deposits of lymph-borne origin must be of considerable magnitude.

Finally, an all-or-none concept of both permeation and embolism is implicit in the prevailing assumption that they are, respectively, continuous and discontinuous processes. However, as demonstrated above, not only embolism but also permeation takes part in the spectrum of discontinuous activities called metastasis. Although individual cases may show either embolism or permeation in a pure form, most cases probably show a variable admixture of both phenomena. Of necessity, the leading phenomenon is embolism, because, as Young (75) stated, it naturally "outstrips" permeation. With time, however, the more quickly formed embolic deposits are caught up by the more slowly formed lines of permeation. Moreover, the embolic deposits themselves may become centers from which new permeation lines spring up. The final picture necessarily combines, to a varying extent, the manifestations of both modes of spread. Consequently, it is unrewarding (if not misleading) to apportion significance to one or another mode of spread in isolation.

REFERENCES

1. Ackerman, L. V., and del Regato, J. U. Cancer: Diagnosis, Treatment and Prognosis, pp. 1060, 1072, 1080. St. Louis: C. V. Mosby Co., 1962.
2. Adler, D., and Fuller, D. Bronchogenic Carcinoma. S. African Med. J., *27:* 841–846, 1953.
3. Altemus, L. R., and Lee, R. E. Carcinomatosis of the Lung with Pulmonary Hypertension. Pathoradiologic Spectrum. Arch. Intern. Med., *119:* 32–38, 1967.
4. Auster, L. S., and Sala, A. M. Causes of Death in Cancer of the Cervix Uteri. Surg. Gynecol. Obstet., *71:* 231–239, 1940.
5. Barnard, W. G., and Robb-Smith, A. H. T. Kettle's Pathology of Tumours, Ed. 3, p. 28. London: H. K. Lewis & Co., Ltd., 1947.
6. Beattie, J. W. Lymphangitis Carcinomatosa. Brit. J. Tuberc. Dis. Chest, *50:* 120–129, 1956.
7. Berenblum, I. The Nature of Tumour Growth. *In:* Lord Florey (ed.), General Pathology, p. 665. London: Lloyd-Luke, 1970.
8. Black, W. A., and Waugh, J. M. The Intramural Extension of Carcinoma of the Descending Colon, Sigmoid, and Rectosigmoid. Surg. Gynecol. Obstet., *87:* 457–464, 1948.
9. Bland-Sutton, J. A Clinical Lecture on Secondary (Metastatic) Carcinoma of the Ovaries. Brit. Med. J., *1:* 1216–1217, 1906.
10. Boyd, W. A Textbook of Pathology, Ed. 8, p. 256. London: Henry Kimpton, 1970.
11. Braunstein, H. Introduction to Neoplasms. *In:* J. G. Brunson and E. A. Gall (eds.), Concepts of Disease, p. 28. New York: Macmillan Co., 1971.
12. Cappell, D. F., and Anderson, J. R. Muir's Textbook of Pathology, Ed. 9, pp. 238, 384. London: Edward Arnold, 1971.
13. Cater, D. B. Basic Pathology and Morbid Histology, p. 265. Bristol: John Wright and Sons, Ltd., 1953.
14. Celis, A., Kuthy, J., and del Castillo, E. The Importance of the Thoracic Duct in the Spread of Malignant Disease. Acta Radiol., *45:* 169–177, 1956.
15 Charache, H. Bronchogenic Carcinoma with Subcutaneous Metastases. Am. J. Cancer, *37:* 431–434, 1939.
16. Cowdry, E. V. Cancer Cells, p. 34. London: W. B. Saunders Co., 1955.
17. Crawford, T. Arteries, Veins and Lymphatics. *In:* G. P. Wright and W. St. Clair Symmers (eds.), Systemic Pathology, Vol. 1, p. 134. London: Longmans, Green & Co., Inc., 1966.
18. Davidson, M. Cancer of the Lung and Other Intrathoracic Tumours, pp. 25–31. Bristol: John Wright and Sons, Ltd., 1930.
19. de Morgan, C. Discussion on Cancer. Trans. Pathol. Soc. London, *25:* 286–306, 1874.
20. Evans, D. M. B. A Case of Squamous-celled Epithelioma of the Bronchus Illustrating Lymphatic Permeation. Lancet, *1:* 1077–1078, 1927.
21. Foulds, L. The Biological Characteristics of Neoplasia. *In:* R. W. Raven (ed.), Cancer, Vol. 1, p. 36. London: Butterworth & Co. (Publishers) Ltd., 1958.
22. Fox, W. A Treatise on Diseases of The Lungs and Pleura, p. 1134. London: J. and A. Churchill, 1891.
23. Fried, B. M. Bronchogenic Carcinoma and Adenoma, p. 89. London: Bailliere, Tindall and Cox, 1948.
24. Galloway, J. The Malignant Diseases of Serous Membranes, p. 48. M. D. Thesis, University of Aberdeen, 1892.
25. Goldberg, G. M. Lymphatics of the Spleen. J. Anat., *92:* 310–313, 1958.
26. Gregg, A. The Golden Gate of Medicine. Ann. Intern. Med., *30:* 810–822, 1949.
27. Grinnell, R. S. Lymphatic Block with Atypical and Retrograde Lymphatic Metastasis and Spread in Carcinoma of the Colon and Rectum. Ann. Surg., *163:* 272–280, 1966.
28. Handley, W. S. Dissemination of Mammary Carcinoma. Brit. Med. J., *1:* 663–664, 1905.
29. Handley, W. S. A Microscopical Study of the Parietal Dissemination of Mammary Carcinoma. Arch. Middlesex Hosp., *5:* 191–222, 1905.
30. Hoggan, G. Cancer in Its Relations to the Lymphatic System. Trans. Pathol. Soc. London, *29:* 384–388, 1878.
31. Irvine, J. P. On the Occurrence of Collapse, Emphysema, and Destructive Pneumonia in Association with Tumours Compressing the Bronchi. Lancet, *1:* 415–416, 1878.
32. Kaplan, N., and Angrist, A. The Mechanism of Jaundice in Cancer of the Pancreas. Surg. Gynecol. Obstet., *77:* 199–204, 1943.
33. Karsner, H. T. Tumors of the Adrenal. Atlas of Tumor Pathology, Fascicle 29, pp. 59–60. Washington, D. C.: Armed Forces Institute of Pathology, 1950.
34. Karsner, H. T. Human Pathology, Ed. 8, pp. 314–315. Philadelphia: J. B. Lippincott Co., 1955.

35. Kettle, E. H. The Pathology of Tumours, p. 32. London: H. K. Lewis & Co., Ltd., 1925.
36. Kline, I. K. Cardiac Lymphatic Involvement by Metastatic Tumor. Cancer, *29:* 799–808, 1972.
37. Kress, M. B., and Allan, W. B. Broncho-alveolar Tumors of the Lung. Bull. Johns Hopkins Hosp., *112:* 115–142, 1963.
38. Lamberta, F., Nareff, M. J., and Schwab, J. Metastatic Carcinoma of the Pericardium. Dis. Chest, *19:* 528–535, 1951.
39. Lynch, R. C., and Docherty, M. B. The Spread of Uterine and Ovarian Carcinoma with Special Reference to the Role of the Fallopian Tube. Surg. Gynecol. Obstet., *80:* 60–65, 1945.
40. Macewen, W. Carcinoma in Its Pathological and Aetiological Aspects, with Remarks on the Principles of Surgical Treatment. Glasgow Med. J., *25:* 271–291, 1886.
41. Meyer, K. K. On Dying of Cancer of the Breast. *In:* A. Segaloff, K. K. Meyer, and S. DeBakey (eds.), Current Concepts in Breast Cancer, pp. 33–34. Baltimore: The Williams & Wilkins Co., 1967.
42. Montgomery, G. L. Textbook of Pathology, Vol. 1, pp. 115–116. Edinburgh: E. and S. Livingstone, 1965.
43. Moore, R. A. A Textbook of Pathology, Ed. 2, pp. 131–132. Philadelphia: W. B. Saunders Co., 1951.
44. Ogilvie, R. F. Pathological Histology, Ed. 5, p. 127. Edinburgh: E. and S. Livingstone, 1957.
45. Onuigbo, W. I. B. Some Observations on the Spread of Lung Cancer in the Body. Brit. J. Cancer, *11:* 175–180, 1957.
46. Onuigbo, W. I. B. Patterns of Metastasis in Lung Cancer: A Review. Cancer Res., *21:* 1077–1085, 1961.
47. Onuigbo, W. I. B. A Mono-block Formalin-fixation Method for Investigating Cancer Metastasis. Z. Krebsforsch., *65:* 209–210, 1963.
48. Onuigbo, W. I. B. Lung Cancer Metastasis to the Pancreas and Its Surrounding Lymph Nodes. Brit. J. Dis. Chest, *60:* 152–155, 1966.
49. Onuigbo, W. I. B. The Organ Status of Lymph Nodes in Cancer Metastasis. Oncology, in press.
50. Pack, G. T., and Brasfield, R. D. Metastatic Carcinoma of the Liver. Am. J. Surg., *90:* 704–716, 1955.
51. Paget, J. Lectures on Surgical Pathology, Ed. 2, Vol. 2, p. 575. London: Longmans, Green & Co., 1853.
52. Pryce, D. M., and Ross, C. F. Ross's Post-mortem Appearances, Ed. 6, p. 168. London: Oxford University Press, 1963.
53. Rawson, A. J. Distribution of the Lymphatics of the Human Kidney as Shown in a Case of Carcinomatous Permeation. Arch. Pathol., *47:* 283–292, 1949.
54. Roberts, O. W. Notes on Malignant Tumours, with Special Reference to 692 Cases. p. 24. M. S. Thesis, University of London, 1928.
55. Robbins, S. L. Textbook of Pathology, Ed. 2, p. 41. Philadelphia: W. B. Saunders Co., 1962.
56. Saphir, O., and Parker, M. L. Linitis Plastica Type of Carcinoma. Surg. Gynecol. Obstet., *76:* 206–213, 1943.
57. Scott, R. W., and Garvin, C. F. Tumors of the Heart and Pericardium. Am. Heart J., *17:* 431–436, 1939.
58. Smithers, D. W. A Clinical Prospect of the Cancer Problem, p. 63. Edinburgh: E. and S. Livingstone, 1960.
59. Spencer, H. The Development and Spread of Lung Cancer, pp. 121–135. Ph.D. Thesis, University of London, 1954.
60. Spencer, H. Pathology of the Lung, pp. 661–668. Oxford: Pergamon Press, Inc., 1962.
61. Stirrat, J. H. Concerning the Mode of Spead of Carcinoma within the Liver. Alberta Med. Bull., *22:* 3–11, 1957.
62. Strauss, B., and Weller, C. Bronchogenic Carcinoma. Arch. Pathol., *63:* 602–611, 1957.
63. Taylor, G. W. Surgical Treatment of Lymph-node Metastases. New Engl. J. Med., *245:* 608–613, 1951.
64. Taylor, G. W., and Nathanson, I. T. Lymph Node Metastases, p. 9. London: Oxford University Press, 1942.
65. Walshe, W. H. Cancer. *In:* W. B. Costello (ed.), The Cyclopedia of Practical Surgery, Vol. 1, p. 619. London: Sherwood, Gilbert and Piper, 1841.
66. Walter, J. B., and Israel, M. S. General Pathology, Ed. 2, p. 560. London: J. and A. Churchill, 1965.
67. Warren, S. Neoplasms. *In:* W. A. D. Anderson (ed.), Pathology, Ed. 4, pp. 456–457. St. Louis: C. V. Mosby Co., 1961.
68. Warren, S., and Meissner, W. A. Neoplasms. *In:* W. A. D. Anderson (ed.), Pathology, Ed. 5, p. 404. St. Louis: C. V. Mosby Co., 1966.
69. Way, S. The Anatomy of the Lymphatic Drainage of the Vulva and Its Influence on the Radical Operation for Carcinoma. Ann. Roy. Coll. Surg. Engl., *3:* 187–209, 1948.
70. Willis, R. A. The Spread of Tumours in the Human Body, pp. 1, 6, 25, 32, 184, 195. London: Butterworth & Co. (Publishers) Ltd., 1952.
71. Willis, R. A. Pathology of Tumours, Ed. 3, pp. 154–156. London: Butterworth & Co. (Publishers) Ltd., 1960.
72. Woodward, J. J. The Toner Lectures. Lecture I. On the Structure of Cancerous Tumors and the Mode in Which Adjacent Parts Are Invaded, p. 10. Washington: Smithsonian Institute, 1873.
73. Yoffey, J. M., and Courtice, F. C. Lymphatics, Lymph and the Lymphomyeloid Complex, pp. 421–422. London: Academic Press, Inc., 1970.
74. Young, J. M. The Thoracic Duct in Malignant Disease. Am J. Pathol., *32:* 253–269, 1956.
75. Young, J. S. Neoplasms. *In:* H. G. Garland and W. Phillips (eds.), Medicine, Vol. 1, pp. 254–263. London: Macmillan Co., 1953.