

- immunoglobulin in clones of diploid human lymphocytes. *Science* 173 (1971) 60
- 73 Blume, R. S., P. R. Glade, H. R. Gralnick, L. N. Chessin, A. T. Haase, S. M. Wolff: The Chediak-Higashi syndrome. Continuous suspension cultures derived from peripheral blood. *Blood* 33 (1969) 821-832
- 74 Conover, J., P. Hathaway, P. R. Glade, K. Hirschhorn: Persistence of phosphoglucomutase (PGM) polymorphism in long-term lymphoid lines. *Proc. Soc. exp. Biol. Med.* 133 (1970) 750-753
- 75 Hirschhorn, K.: Personal communication
- 76 Choi, K. W., A. D. Bloom: Biochemically marked lymphocytoid lines: Establishment of Lesch-Nyhan cells. *Science* 170 (1970) 89-90
- 77 O'Brien, J. S., S. Okada, M. W. Ho et al.: Ganglioside storage diseases. *Fed. Proc.* 30 (1971) 956-969
- 78 Glade, P. R., S. W. Broder: Preparation and care of established human lymphoid cell lines. *In Vitro Methods in Cell-mediated Immunity*. (Ed. B. R. Bloom and P. R. Glade.) Acad. Press Inc. New York (1971)
- 79 Bernaco, D., P. R. Glade, S. W. Broder, V. C. Migliano, K. Hirschhorn, R. Ceppellini: Stability of H-LA and appearance of other antigens (LIVA) at the surface of lymphoblasts grown *in vitro*. *Fol. Hemat.* 54 (1969) 795-812
- 80 Flier, J. S., P. R. Glade, S. W. Broder, K. Hirschhorn: Lymphocyte stimulation by allogeneic and autochthonous cultured lymphoid cells. *Cellular Immunol.* 1 (1970) 596-602
- 81 Reisfeld, R. A., B. D. Kahon: Biological and chemical characterization of human histocompatibility antigens. *Fed. Proc.* 29 (1970) 2034-2040
- 82 Epstein, M. A., B. D. Achong, Y. M. Barr: Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* 1964/I, 702
- 83 Evans, A. S., J. C. Niederman, R. W. McCollum: Seroepidemiologic studies of infectious mononucleosis with EB virus. *New Engl. J. Med.* 279 (1968) 1121-1127
- 84 Henle, G., W. Henle: Immunofluorescence in cells derived from Burkitt's lymphoma. *J. Bacteriol.* 91 (1966) 1248-1256
- 85 De-The, G., J. C. Ambrosioni, H. C. Ho, H. C. Kwan: Lymphoblastoid transformation and presence of herpes-type viral particles in a chinese nasopharyngeal tumor culture *in vitro*. *Nature* 221 (1969) 770-771
- 86 Hirshaut, Y., P. R. Glade, L. Octavio, B. D. Vieira, E. Aimbender, B. Dvorak, L. E. Siltzbach: Sarcoidosis, another disease associated with Herpes-like virus infection. *New Engl. J. Med.* 283 (1970) 502-505
- 87 Gerber, P., J. Whang-Peng, J. H. Monroe: Transformation and chromosome changes induced by Epstein-Barr virus in normal human leucocyte cultures. *Proc. nat. Acad. Sci. (Wash.)* 63 (1969) 740-747
- 88 Papageorgiou, P. S., C. Sorokin, K. Kouzoutzakoglou, P. R. Glade: Herpes-like Epstein-Barr virus in leprosy. *Nature* 231 (1971) 47-49

P. S. Papageorgiou, M.D., Dept. of Pediatrics, Div. of Infect. Dis., Mount Sinai School of Med. of the City Univ. of New York, New York, 10029

EDITORIAL

Lymphology 5 (1972) 89-93
© Georg Thieme Verlag, Stuttgart

The Place of Lymphadenectomy in Cancer Surgery

G. Crile, Jr.

Department of General Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio

History of Lymphadenectomy

The principle of removing regional lymph nodes along with the primary cancer was established in England, in 1867, by a surgeon named *Moore*, who was the first to perform a radical mastectomy. For the next century surgeons devoted their energies to devising more and more radical operations designed to remove more and more of the nodes that drained the tumors. Few voices were raised in opposition to this policy, because it seemed too be logical. Yet in 1898 *Rudolph Matas*, in a discussion of one of Halsted's papers, said that his "3 years cures" had been 41% with the old "incomplete" operation and only 38.3% with the new Halsted type of radical mastectomy (1).

Natural History of Cancer

It is easy to calculate that the routine removal of regional nodes in patients with cancer of the breast cannot greatly increase the crude rate of survival. If, for example, there were 100 patients with breast cancer 75 of them might be considered to be operable. Forty of these 75 would have no involvement of nodes and could not be benefited by removing nodes. Thirty-five of the patients would have nodal metastasis, but 28 (80%) of the 35 with involved nodes would ultimately die of cancer in spite of having had a radical mastectomy. This leaves only 7 of the original 100 who might have been cured by removing the nodes. Thus 7% is the improvement in survival that can accrue from routine removal of nodes. And this takes no account of the fact that the rate of survival is just as high when nodes are not removed until the metastases in them become palpable as it is when the nodes are removed before they are palpably involved.

In cancer of the breast the routine performance of radical mastectomy often causes swelling of the arm, limitation of motion of the shoulder and discomfort and deformity of the chest wall. Radical neck dissection causes deformity of the neck, shoulder drop and often paralysis of the inframandibular branch of the facial nerve as well as a significant immediate mortality. Radical dissection of the groin is apt to cause massive and sometimes disabling edema of the leg. Combined abdominoperineal resection of the rectum results in a permanent colostomy and an immediate mortality that is estimated to be about 10% in the hands of the average general surgeon. Radical pancreaticoduodenectomy done for cancer of the ampulla of Vater rarely effects a cure but involves an immediate mortality rate of 10% in the hands of expert surgeons and as high as 40% in some reported series. Are these massive, dangerous and damaging attacks on the regional nodes justified in terms of increased survival? And even more important does the removal of uninvolved nodes weaken the immunologic defenses of the host and promote the growth of metastases? Finally, is irradiation an acceptable substitute for radical operations, or does it share their disadvantages in increasing morbidity and decreasing the host's resistance to the spread of the cancer? In order to answer these questions we must examine the natural history of cancer.

There are two main types of cancer. The most common is the type, that like cancers of the breast, kills by distant metastasis. These cancers tend to invade both blood vessels and lymphatics early, often long before the tumor is recognized, so that distant metastasis is already present when treatment is given. That is the reason why radical resection of involved nodes does not often effect a cure. The involvement of the nodes is more a sign that the disease is incurable than a challenge to perform an ultraradical operation. Yet if only a few nodes are involved there is still a chance of cure. Usually this chance is just as good following conservative operations on the nodes in which nerves and muscles are not sacrificed, as after the most radical and deforming procedures and radiation too. The reason is that when more than 3 or 4 nodes are involved distant metastases are almost always present, and no operation designed to eradicate the local disease can affect the ultimate course of the disease. An exception to this rule is papillary carcinoma of the thyroid, a strange type of cancer that usually runs a benign course even when 20 or 30 nodes are involved.

The second type of cancer is typified by squamous cell cancer of the head and neck which tends to remain localized to the primary site and the field of lymphatic drainage and often kills by local extension rather than by systemic metastasis. It is in the treatment of this kind of cancer that radical lymphadenectomy of the type described at the turn of the century by Crile, has had its best results. But this operation was designed in a day when most of the cancers were advanced and when the metastases usually had penetrated the capsules of the nodes and invaded muscles, necessitating sacrifice of nerves and muscles. Yet today, when cancers are treated much earlier, the same destructive operation is often done routinely as an elective procedure in patients who have no palpable involvement of nodes. In short, like radical mastectomy, it has become standardized and accepted as the orthodox treatment of cancers of the head and neck regardless of the stage of the disease. Furthermore, most studies have shown no advantage to removal of nodes that do not appear to be involved provided the patient is followed and the nodes are removed if involvement appears.

Present Attitudes Towards Lymphadenectomy

Radical mastectomy and radical dissection of the neck are operations that produce considerable disfigurement and morbidity but which do not involve a high risk of immediate mortality. On the other hand, combined abdominoperineal resection for rectal cancer involves not only the morbidity of a colostomy, but also a high mortality of 5 to 15%. Even in the hands of specialists the mortality of the operation when done for low-lying cancers is rarely less than 3%. The question is, if the primary tumor can be destroyed locally by electrocoagulation is there any advantage in resecting the rectum to remove the nodes. The answer is no, unless the surgeon can operate with a mortality rate under 3%. When nodes are involved, the rate of cure is so low that the risk of postoperative death exceeds it. The following are the figures from the Cleveland Clinic.

Only 35% of the patients with low-lying rectal cancers have involvement of nodes. Only 20% of those with involved nodes are permanently cured of cancer. Thus only 1 in 15 or 7% of the patients treated by resection would do better than if their primary tumors were destroyed by coagulation and the nodes were disregarded.

It is clear that the radical operation is a failure if its mortality rate is 10% and only 7% of the patients are benefitted by it. At the Cleveland Clinic the immediate mortality of the operation is only 4% but 1% more die of late complications of the operation such as perforation of the colon or intestinal obstruction. These deaths are within days or a few weeks of the time of operation, whereas patients with involved nodes may live 5 to 10 years before dying of cancer. In fact, the period of survival of patients ultimately dying of cancer is a year longer in patients treated by coagulation than in those treated by resection and abdominal carcinomatosis does not occur. Thus in terms of man-years of survival one would have to operate with a mortality of less than 3% if resection of the rectum were to be as effective as electrocoagulation.

Radical pancreaticoduodenectomy for carcinoma of the ampulla of Vater is another operation that carries a high mortality and a low rate of cure. One can easily calculate that unless the surgeon's mortality rate less than 10% (as stated some reported mortalities are as high as 40%) the man-year survival of his patients would be greater following

bypass, or in patients with polypoid tumors bypass and electrocoagulation than following the radical operation. This is especially true of older patients whose life expectancy is not long and in whom the risk of operation is increased. Yet often the orthodox operation is done, even on people in their late sixties and seventies, and their deaths are accepted as inevitable sacrifices to the attempt to cure.

The Role of the Regional Node in Tumor Immunity

It is now more than 18 years since *Mitchison* reported that when lymphocytes from the regional nodes that drained a tumor were transplanted to another mouse of the same strain they immunized the new mouse against the cancer. Lymphocytes from contralateral nodes, circulating lymphocytes, and lymphocytes from the spleen had no such effect (2).

These observations suggested that removal of immunized nodes might diminish the resistance of the host to the spread of metastasis. In a murine system, reported in 1965, this was found to be the case. If uninvolved regional nodes were removed or irradiated at the time the mouse's tumor-bearing foot was amputated the incidence of metastasis was greatly increased (3). Clinical studies on patients with breast cancer likewise showed that prophylactic removal of uninvolved nodes resulted in a 15% lower 5 year survival rate than when the nodes were left alone. When nodes were involved, it made no difference whether or not they were removed early, before the metastasis was palpable, or later when the metastasis appeared (4). The 5 year survival rate was identical in both groups. Thus there appeared to be sound laboratory evidence in favor of not treating nodes that did not appear to be involved.

As evidence that the striking increase in metastasis that occurred when sensitized nodes were removed is not a phenomenon peculiar to transplantable tumors of mice, *in vitro* studies have shown that lymphocytes taken from uninvolved axillary nodes attack and destroy cancer cells taken from the primary tumor. Both the lymphocytes from the axillary nodes and the cells from the primary cancer are put into tissue culture. Soon the sensitized lymphocytes can be seen clumping about the cancer cells making rosettes around them and destroying the cells. On the other hand, lymphocytes from the axillary nodes of patients with extensive axillary metastases gave no such reaction and showed no tendency to attack the cancer cells (5).

Conclusion

In summary it seems clear that there has been a great overemphasis of the importance of removing the regional lymph nodes of patients with cancer. Not only is the morbidity and mortality of treatment increased by the routine performance of radical operations, but it is also likely that removing or irradiating uninvolved nodes promotes the dissemination and growth of metastases. The whole subject of radical lymphadenectomy is open for critical re-evaluation. It is my belief that sound statistical studies will indicate that elective lymphadenectomy should not be done in the treatment of cancers whose regional nodes are accessible to palpation, and that when involved nodes are removed conservative operations are just as effective as the most radical ones.

References

- 1 *Matas, R.*: Personal experience, with remarks on the operative treatment of cancer of the breast. *Trans. Amer. surg. Ass.* 16 (1898) 165-181
- 2 *Mitchison, N. A.*: Passive transfer of transplantation immunity. *Proc. roy. Soc. Lond.* 142 (1954) 72-87
- 3 *Crile, G., jr.*: Rationale of simple mastectomy for clinical stage I cancer of the breast. *Surg. Gynec. Obstet.* 120 (1965) 975-982
- 4 *Crile, G., jr.*: Treatment of cancer of the breast. *Cleveland Clinic Quarterly* 38 (1971) 47-54
- 5 *Deodhar, S. D., G. Crile jr., C. B. Esselstyn jr.*: A study of the tumor cell-lymphocyte interaction in patients with breast cancer. Pending publication, *Cancer.*

G. Crile, jr., M.D., Dept. of General Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio

BOOK REVIEW

KUISK, H.: Technique of Lymphography and Principles of Interpretation. (W. H. Green, Inc., St. Louis, Mo., U.S.A.) 1971. 319 p., 155 figs.

This book constitutes the first trial to give a comprehensive review of the considerable but very scattered and dispersed information available in the medical literature concerning lymphography. After about a decade of clinical application of this specialized radiographic measure on a widespread scale, such a monography should be very welcome.

In 22 chapters the author deals successively with the technique and complications of lymphography, lymphographic anatomy of the inguinal, pelvic and abdomino-aortic lymphatic systems. Extensive attention is paid to the different sites and technical modalities of the injection of the contrastmedium. In addition to the pedal lymphography, very complete chapters cover respectively testicular, penile, mammo, cervical and intra-nodal lymphography as well as brachiolymphography and indirect (subcutaneous submucosal intra-muscular and intra-cavity) lymphography.

The final part of the book deals with the interpretation of lymphograms. Considering the importance of this aspect of lymphography it is rather surprising that only about 60 pages of the volume are devoted to this problem.

Although concise this chapter can nevertheless be considered to be complete and to give a good over-all review of the problem. The criteria for interpretation as stated by the author are objective and sound.

The text is clearly written in a logical and systemic arrangement. The literature review on each subject is very extensive and appropriate. In addition the author tries to make a synthesis at the end of each chapter based on his personal experience as well as on the opinions of the different cited authors. A much needed evaluation of the value of lymphography in the detection of metastases of tumors of epithelial origin is lacking and this can be considered as a minor drawback of this book. The illustrations are numerous and adequate, covering all important and typical images in the field. However the quality of many reproductions is rather poor, so that some information seems to be lost.

In summary this book should be recommended without any doubt, to any radiologist or clinician interested in the field of lymphography. For students and residents it constitutes a basic volume that can be successfully consulted on all aspects of lymphography. It should therefore be present in the library of each radiology training department. A. BEART