The Pathology of Tumors
Part I: Precancerous and Pseudomalignant Lesions

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Introduction
The scope of these articles on the pathology of cancer will not fall within the usual range of information found in standard textbooks. Their purpose is to present a broad perspective of representative material on the relationship of pathology to diagnosis, treatment and prognosis which will be helpful to the physician and the medical student. Only representative examples of various pathologic processes are presented; stress is given to the practical application of pathology and the need for a cooperative attitude between physician and pathologist.

Probably the most important decision a surgical pathologist has to make about every neoplasm he studies is whether or not it is benign or malignant. It is well to emphasize that in making this decision, he is referring to a biological rather than to a morphological concept. In other words, when the pathologist calls a tumor “malignant,” he is implying that this tumor, regardless of how innocuous it may look under the microscope, has the capacity to invade local tissues and, in most instances, to give rise to distant metastases. Conversely, when he calls a tumor “benign,” he is implying that the lesion, regardless of how ominous it may look, is not capable of producing distant metastases and that it will not endanger the life of the patient unless it is located in a strategic position or endowed with some peculiar secretory property.

The criteria used by the pathologist to make this biological distinction are, to be sure, morphological. As a rule, a benign tumor is well-circumscribed or encapsulated; microscopically, it grows in an orderly fashion and is composed of cells closely resembling those of its parent tissue. Conversely, a typical malignant tumor invades the organs from which it arose and eventually the surrounding tissues; it is made up of cells that vary prominently in size and shape; large, hyperchromatic nuclei and prominent nucleoli are common; mitotic figures are numerous, and some are atypical; permeation of lymph or blood vessels by tumor cells may be present.

It would be easy for the surgical pathologist if the morphology and biological behavior of all tumors went hand in hand in this fashion in every case. Unfortunately, they do not. The exceptions are so many that a careful clinicopathologic study of a large number of cases has

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This is the first of a four-part feature, which will appear in consecutive issues of Ca.
been necessary to define the criteria of malignancy for each organ involved; within a given organ, for each type of tumor; and within a given tumor, for each morphologic variant. This approach has revealed that some microscopic features that are useful in the evaluation of certain tumors are meaningless in others. A few examples will illustrate this point. A capillary hemangioma in a child may have numerous mitotic figures, yet it is a perfectly benign lesion, which will regress spontaneously in most cases; on the contrary, the presence of even a moderate number of mitoses in a smooth muscle tumor of the gastrointestinal tract is highly suggestive that this tumor is a leiomyosarcoma. Bizarre nuclear forms and large nucleoli have no prognostic significance in most endocrine tumors (Fig. 1), whereas if they are present in a prostatic lesion, they are practically always diagnostic of carcinoma (Fig. 2). Binucleate or somewhat atypical chondrocytes are of no significance if found in a nucleus pulposus, in a specimen of synovial chondromatosis, or in a soft tissue cartilaginous lesion of the hand, but they may be the only signs of malignancy in a cartilaginous tumor of the pelvis or long bone. A feature apparently as trivial as a psammoma body (a small calcified round structure with concentric laminations present in the stroma) is of no concern if found in a benign meningeal or ovarian tumor. Yet its presence in a thyroid lesion is highly suggestive of carcinoma and, if found in an otherwise normal section of thyroid, should make the pathologist suspect that a carcinoma may be present a few microns away (Fig. 3).

Epithelial structures inside a lymph node, which would seem unquestionable proof of metastatic carcinoma, may sometimes represent a perfectly benign process.

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Normal endometrial glands (Fig. 4), thyroid follicles, lobules of mammary tissue and clusters of melanocytes may be found within lymph nodes, without having any malignant connotation. It is often imperative for the pathologist to have detailed clinical and radiological information, because this may be of great importance in the evaluation of the microscopic section. This information will have greater or lesser weight depend-
Fig. 3. Several psammoma bodies appearing in the stroma of a papillary thyroid carcinoma as dark round structures. They are practically never present in benign thyroid glands.

Fig. 4. Normal endometrial glands inside a pelvic lymph node, occurring in a patient with advanced endometriosis.

ing on the circumstances. There is no difficulty in making a microscopic diagnosis of a poorly differentiated epidermoid carcinoma. On the other hand, the presence of exuberant and somewhat atypical osteoid formation seen in a fracture callus or in myositis ossificans may lead the pathologist to believe that he is dealing with an osteosarcoma, unless he is aware of the clinical and radiologic features of the case. A verrucous carcinoma of the oral cavity is a tumor so highly differentiated that unless the pathologist knows the lesion has invaded adjacent areas, such as the soft tissues of the cheek or mandible, he is likely to diagnose the tumor as papilloma, hyperkeratosis or some other benign process. The difference between Bowen's disease and certain types of actinic keratosis lies not so much in its microscopic appearance as in the location, site and clinical appearance of the lesion. Deciding whether a thymoma is benign or malignant is usually done not on the basis of the histology, but rather on the encapsulated versus infiltrative type of growth as determined grossly at operation. Some thyroid follicular adenocarcinomas metastatic to bone, and some chondrosarcomas growing in soft tissue, are so well differentiated that they simulate normal thyroid gland and normal cartilaginous tissue, respectively (Fig. 5).

The above mentioned examples should be enough to convince anybody of the extreme importance of providing the pathologist with complete and accurate clinical information on every case. Unfortunately, this responsibility is too often forgotten or delegated to an intern or a nurse who is frequently not familiar with the case. Perhaps some clinicians are still under the misconception that a pathologic examination is something like a serum potassium determination, in which all the pathologist needs is a properly identified sample. Nothing is further from the truth; disastrous and totally unnecessary errors may be the consequence of this attitude, which sometimes borders on medical irresponsibility.

It goes without saying that the morphologic features that are known to be important in determining the natural history of a tumor should be individualized and separated from all the vagaries of growth that some tumors may present, and which are of no practical significance. The histologic interpretation of these vagaries may present a challenge and at times can provide a clue to the origin of a tumor, but they are certainly of no help to the pathologist in predicting its biological behavior. It makes no difference to the patient or the surgeon if a breast fibroadenoma is intracanalicular or pericanal-
icular, if a basal cell carcinoma is solid, keratotic or adenoid, if an osteosarcoma is osteoblastic, chondroblastic or fibroblastic, or if a granulosa cell tumor of ovary is folliculoid, adenomatoid, cylin-
droid, trabecular or sarcomatoid. It is important for the pathologist to realize this fact, and not emphasize subclassifications which are clinically unimportant. Otherwise, the surgeon may be led to believe that histologic subclassifications of tumors are always consequential and are to be disregarded. Nothing could be further from the truth. There is, for in-

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stance, a marked difference in prognosis between a myxoid and a round cell liposarcoma, between an alveolar and a pleomorphic rhabdomyosarcoma and between a mucinous and signet ring cell type breast carcinoma.9-11

In addition to a correct diagnosis of the type of tumor and, if useful, a subclassification of it, there is much more information the pathologist can give to the clinician. He should describe the extent of involvement and the adequacy of the surgical excision. Features of prognostic importance, such as the depth of dermal invasion in a malignant melanoma; pushing vs. infiltrative pattern of growth in a laryngeal epidermoid carcinoma; presence of vascular invasion in large bowel adenocarcinomas, and so on should always be looked for and reported. If the choice of therapy is influenced by the microscopic typing or subtyping, it is better to adapt the terminology to this purpose. For instance, in our institutions well differentiated endometrial adenocarcinomas are treated surgically, with no previous radiotherapy, unless the uterus is enlarged. Conversely, poorly differentiated adenocarcinomas receive preoperative radiation therapy routinely, regardless of the size of the uterus. We therefore call all endometrial adenocarcinomas either well or poorly differentiated, instead of subdividing them into three or four grades.

Finally, it should be remembered that although morphology is a very important criterion for predicting the natural history of a tumor, age, sex, location and many other factors also play a significant role. Histologically identical epidermoid carcinomas of skin and uterine cervix behave in a completely different fashion. The five-year survival rate for osteosarcomas of tibia is 37 percent, whereas in osteosarcoma of the axial skeleton the five-year survival is only six percent.12 The prognosis of thyroid carcinomas is better in children than in adults, and the prognosis of malignant melanomas is better in females than in males.

Only by continuously evaluating these numerous factors will the tumor pathologist satisfactorily perform his prime function, which is to collaborate with the clinician toward providing every patient with the best possible treatment.

Precancerous Lesions

There are a number of specific pathologic processes that have been designated as
precancerous. It is unfortunate that the term has been applied indiscriminately to many lesions that have variable potentialities. In the large and heterogeneous group of lesions that are known to predispose to cancer, there are some in which cancer is inevitable, whereas in others the incidence of malignant transformation is so low that the risk of cancer can be disregarded in the management of the case. It is obvious that instead of grouping all these lesions together under the generic term of "precancerous," one needs to evaluate the risk of malignant transformation for each lesion according to the extension, duration and other determinants. Polyps of the large bowel are a good example of the prominent differences in malignant potential between superficially similar lesions.

Patients with familial polyposis, a disease with an autosomal dominant type of inheritance, develop adenocarcinomas with mathematically regularity, usually in their early thirties (Fig. 6). Therefore in an individual with this disease it is mandatory to consider total colectomy. Villous adenomas are usually solitary tumors presenting more often in the rectosigmoid area (Fig. 7). In time, a high percentage of villous adenomas will develop an area of invasive adenocarcinoma. The larger villous adenomas carry a proportionately greater risk. These neoplasms should, therefore, be removed in toto as soon as they are detected.

A different problem arises in adenomatous polyps, which make up a large fraction of the polyps of the large intestine. It now seems clear that the precancerous nature of this lesion has been overestimated and overemphasized, and as a result, unnecessary radical operations have been performed for a growth that in the large majority of the cases behaves in a benign fashion. We do not deny the fact that invasive adenocarcinomas may, on occasion, arise from adenomatous polyps. What we are concerned with is how often this phenomenon occurs and how this fact should influence the management of the patient. Microscopic examination of the tip of an adenomatous polyp will often show some degree of epithelial atypia,
even to the point where it might be called "carcinoma in situ" (Fig. 8). However, no matter how atypical the cells look, polypectomy will invariably be curative as long as the proliferation remains above the level of the muscularis mucosae. Apparently the reason for the invariable absence of metastases under these circumstances is that the lamina propria of the large bowel mucosa does not contain lymphatic vessels. Even if the stroma of the polyp is infiltrated by tumor cells, a simple polypectomy will be adequate treatment, provided that the stalk of the polyp is free of tumor, and the tumor is not undifferentiated, because the incidence of lymph node metastases in these cases is extremely low. Accurate determination of stalk invasion by tumor requires that the polyp be removed intact and be processed and oriented properly. This important evaluation is sometimes impossible to make if the polyp is removed in pieces with the fiberopticscope. The idea that a substantial number of colonic carcinomas arise from adenomatous polyps has yet to be substantiated. Polyps and carcinomas do not have the same distribution within the colon and careful study of small carcinomas usually fails to reveal remnants of a pre-existing polyp.

At the lower end of the spectrum of colonic polyps are those of the retention and hyperplastic (or metaplastic) type (Figs. 9 and 10). Both of these are completely free of malignant potential.

A lesion which can be truly called precancerous is xeroderma pigmentosum. This cutaneous disorder presents in children as the result of undue sensitivity to ultraviolet light. It is characterized by skin atrophy, mottled pigmentation and telangiectases and is associated with the inevitable development of skin cancer (Fig. 11). Basal cell carcinoma, epidermoid carcinoma and even malignant melanoma may occur and eventually cause the death of the child before the age of twenty.

Hutchinson's freckle, a flat, pigmented lesion most commonly located in the cheek of elderly patients, is another forerunner of malignancy (Fig. 12). By the time these growths are excised, many of them already contain an invasive malignant melanoma in their center. It is likely that if Hutchinson's freckles are left untreated, and the
Fig. 10: Microscopic pattern of a retention polyp. The multiple small cysts lined by low epithelium, abundant stroma and ulcerated surface are characteristic. This type of polyp is probably not a neoplasm.

Fig. 11: Child with xeroderma pigmentosum. Several invasive carcinomas are already present.

individual who harbors them lives long enough, every one of them would eventually be complicated by the development of an invasive malignant melanoma. Although these melanomas are biologically less aggressive than those arising de novo, it is necessary to remove Hutchinson's freckle in order to prevent this complication.

The so-called "leukoplakia" of mucous membranes is another lesion for which the malignant potential has been greatly overestimated (Fig. 13). First of all, the term is a rather inclusive one and refers more to a clinical rather than to a microscopic concept. Since the only important prognostic feature of these lesions is the presence and degree of epithelial atypia, we have chosen to call them epithelial hyperplasias or keratoses, and grade the atypia, if present at all, as mild, moderate or severe. The assumption, of course, is that the more pronounced the atypia, the greater the likelihood of developing carcinoma. It should be realized, however, that even in patients with the severely atypical forms of this disease, the incidence of invasive cancer is low. This is true for lesions of the oral cavity, larynx and vulva. For instance, Pindborg et al. followed 248 patients with oral leukoplakia for one to 10 years: only 4.4 percent developed epidermoid carcinoma. We followed 84 patients in whom a biopsy of the larynx had shown keratosis, with varying degrees of atypia; only three developed invasive epidermoid carcinoma. These figures indicate that lesions of leukoplakia or keratosis should be biopsied for evaluation and that the patient should be followed, especially if the biopsy shows severe atypia, but that there is no need for aggressive prophylactic anticancer therapy.

A lesion somewhat similar to leuko-
plakia but occurring in sun-exposed areas of the skin is solar or actinic keratosis (Fig. 14). This also can become epidermoid carcinoma; however, the risk is low and the tumors that arise from this lesion have a low grade of malignancy.  

In lesions such as dysplasia of the uterine cervix (Fig. 15), adenomatous hyperplasia of endometrium and hydatidiform mole, a relationship with malignancy (that is, epidermoid carcinoma in the first case, adenocarcinoma in the second and choriocarcinoma in the third) is known to exist. However, the low incidence of cancer in these lesions and its easy detection allow the clinician to safely follow a conservative course, by performing Papanicolaou smears in the first case, repeat curettages in the second, and chorionic gonadotropin determinations in the third, without immediately adopting a surgical or chemotherapeutic treatment.

Paget’s disease of bone and von Recklinghausen’s neurofibromatosis are also known to be associated with cancer: osteosarcoma and other bone tumors in the first case, and malignant schwannoma in the second. The incidence of malignant schwannoma in von Recklinghausen’s disease is usually reported at about 10 percent, but is actually much less. Unfortunately, there is nothing a physician can do to prevent this occurrence. Even if every one of the innumerable neurofibromas present in these patients were excised, nothing would be accomplished because the malignant schwannomas in von Recklinghausen’s disease nearly always arise from deep, large nerve trunks, such as the sciatic or the vagus nerve, rather than from the little pedunculated growths in the skin.

At the lower end of the spectrum are lesions such as pigmented junctional nevi of skin (Fig. 16), fibrocystic disease of breast, lithiasis of gallbladder, osteochondromas of bones, endemio goiter and cystic endometrial hyperplasia, in which the evidence of an increased incidence of malignancy is at best controversial.

In dealing with “precancerous” lesions, the physician must ask himself, “Does this lesion inevitably become cancer?” If the answer is “yes,” appropriate
measures should be taken without delay; if the answer is "sometimes," then the location of the lesion, its extent and the probability of its becoming cancer should be resolved before definite therapy is instituted.

Benign Lesions That Resemble Cancer
We have already mentioned that the morphology and biological behavior of tumors do not always coincide. While delay in treatment is sometimes caused by deceptive microscopic appearance of a malignant tumor it is also true that drastic surgical procedures are occasionally performed for perfectly benign lesions because of their ominous appearance. Many of the latter, most of which are not even neoplastic, have been delineated only in the last few years. What follows are only some examples of a list too long to be enumerated here.

Keratoacanthoma, a self-healing skin nodule, possibly of viral etiology, and pseudoepitheliomatous hyperplasia, an epithelial reaction to various dermal processes, both simulate epidermoid carcinoma (Fig. 17). Spindle and epithelioid cell nevi (also known as Spitz's nevi and juvenile melanomas) are simply exuberant compound nevi, commonly, although not exclusively, seen in children as elevated pink nodules. Cellular blue nevi are usually situated in the sacrococcygeal area and can attain large size; both have been confused with malignant melanoma.

Myositis ossificans (Fig. 18), proliferative myositis (Fig. 19) and nodular fasciitis can simulate osteosarcoma, rhabdomyosarcoma and fibrosarcoma, respectively. Organizing and recanalizing thrombi in veins (so-called Masson's hemangiomas) are still being confused with angiosarcomas (Fig. 20). Sclerosing adenosis and nipple adenomas have resulted in a number of unnecessary mastectomies because of their complicated proliferative pattern (Fig. 21). Some benign vaginal polyps seen in adult women have a superficial resemblance to botryoid rhabdomyosarcoma, a highly malignant tumor.

For one who has not seen the histo-
pathologic appearance at the site of an insect bite in the skin, it would be hard to believe that this lesion can simulate both epidermoid carcinoma and malignant lymphoma, yet that is the case. The peculiar microglandular hyperplasia of the endocervix12 (Fig. 22) and the bizarre nuclear alterations of the endometrial stroma, seen not infrequently in women who take birth control pills, may attain a pseudocarcinomatous and pseudosarcomatous appearance, respectively. A marked degree of reticular or lymphocytic hyperplasia, up to a point of simulating lymphoma, can be seen in lymph nodes in patients with infectious mononucleosis, herpes zoster, brucellosis, rheumatoid arthritis and reaction to vaccination, or in patients receiving anticonvulsive drugs.13 Malignant lymphoma can also be simulated by massive accumulations of lymphocytes in extranodal sites, including the lung (Fig. 23), mediastinum, stomach, bowel and skin14 (Fig. 24). This condition is designated as pseudolymphoma or lymphoid hyperplasia.

Summary

The biological behavior of a tumor is the clinician's, patient's, and must be the pathologist's main concern. Predicting this behavior accurately requires clinical as well as microscopic information since the morphology of a tumor may be inconsistent with its true nature.

The pathologist's final decision should be communicated in terms most useful to the surgeon, avoiding emphasis on subclassifications, except where they are clinically significant, and adapting the terminology so that, in those situations where typing or subtyping may influence the choice of therapy, the recommendations are clear to the surgeon.

Evaluating precancerous conditions and benign tumors that resemble cancer creates special problems for the pathologist. Many conditions previously designated as "precancerous" have, in fact, a very low potential for malignant development and only extreme care in assessing these lesions will prevent unnecessary surgery for a truly benign condition or conservative management of a condition which will inevitably become cancer.

There are a number of lesions, many of which are not even neoplastic, that microscopically resemble cancer. Here again the pathologist must exercise great care that drastic surgery is not performed for a perfectly benign lesion with an ominous appearance, or that treatment of cancer is not delayed.

Fig. 16: Three different areas from a case of myositis ossificans, illustrating the maturation sequence of this lesion. The deeper areas are undifferentiated and can simulate sarcoma (top). Formation of osteoid can be detected immediately above (center). The more peripheral areas show well-organized bone production (bottom).
Fig. 19: Microscopic appearance of proliferative myositis. Large, ganglion-like cells are seen separating the skeletal muscle fibers.

Fig. 20: So-called Masson's hemangioma. This simply represents organizing and recanalizing thrombosis in a vein, but because of the complicated pattern it may be confused with angiosarcoma.

Fig. 21: Adenoma of nipple. A complicated proliferation of glandular structures extends to the skin surface. This lesion simulates breast cancer clinically as well as microscopically.

Fig. 22: Proliferation of small glands in the endocervix of a patient taking contraceptive pills.

Fig. 23: Gross appearance of pseudolymphoma of the lung. The bronchi and vessels are separated but not destroyed by a poorly circumscribed zone of consolidation. The alveoli are obliterated. The hilar lymph nodes showed only hyperplasia.

Fig. 24: Pseudolymphoma of skin, also known as lymphocytoma cutis and cutaneous lymphoid hyperplasia. The presence of lymphoid follicles with germinal centers is the more important sign to distinguish this lesion from malignant lymphoma.
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