Öbersichten

Transformation of Malignant Growth*

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Summary. In the present paper, the distinction of carcinomatous and sarcomatous growth will be discussed at the cellular level.

The characteristics of the cancer cell are generally accepted as stable by nature. This agrees well with experiences of studies of cancer in the research laboratory and the clinic, without encountering significant contradictions. On the other hand, during the research of malignant growth at the cellular level for about 27 years using Yoshida sarcoma (since 1943) and ascites hepatomas (since 1951), it has been observed that individual constituent cells of malignant growth were continuously fluctuating, within a certain limit as a rule, and in some cases, an entirely unanticipated transformation of the morphological pattern of sarcoma into that of carcinoma, owing to the change on the part of the cell, took place. This transformation was occasionally accompanied with significant reduction in the speed of the growth.


I. Cancerization and Initial Cancer Growth

In 1867, Waldeyer [1] demonstrated definitely the fact that the cancer cell originates by the change—cancerization—of the normal somatic cell. Before him, Thiersch (1865) and several other pathologists had pursued the same line and obtained the same result. This achievement of German pathologists, about 100 years ago, provided a fundamental basis for scientific research of cancer that continues to today. Yamagiva’s success [2, 3] (1915) in inducing experimental skin carcinoma in the ear of the rabbit by coal tar painting and the description of histogenesis of this carcinoma, from the early stage up to carcinomatous change, confirmed beautifully the Waldeyer’s observation of carcinogenesis in man.

Thus, the concept of “cancerization” of normal somatic cell was firmly established. However, this cancerization is a phenomenon which is beyond the human observation. There is no way to know exactly how large a number of original cancer cells which serve as the starting elements for cancer growth would originate, and how they would continue to grow, in the earliest stage of cancer development. This is the stage preceding the visible tumor formation, with which a cancer is first recognized in reality. This stage may, therefore, be regarded as something like mythological age in the history of the development of cancer.

A tumor formation, regardless of its size, is originally a colony of cancer cells, that is, the result of continued multiplication of the initial cancer cell(s) originating from cancerization of a somatic cell. This tumor is accessible for investigations, but the process of cancerization is already completed and the related problems are no longer involved in it. It can present only problems relating to the growth of established cancer cells.

It may be natural to deem that the cancerization and the growth of “cancerized” cells are two unrelated events in the earliest stage of cancer development. This is indicated, first of all, by the fact that the causative agents for cancerization, such as chemical carcinogens or radioactivities, often show inhibiting effect on the growth of cancer. In this relation, it may be possible to realize a situation that the biological condition of the host tissue where the initial cancer cells originated proves itself incompatible with, at least, some of these “changed” cells which acquired a characteristics of the cancer cell, so that they might be eliminated, in the end, without contributing to the tumor formation.

This problem of the host condition for the initial cancer growth preceding tumor formation is, as stated above, beyond close examination but could be connected, to some extent, with the studies of the so-called host-tumor relation, which are carried on in the laboratory with established tumors. However, cancerization of a normal cell is unique. It is not accessible

* The author dealt with the subject on the same line in the XII Maude Abbott lecture of the International Academy of Pathology given in 1969. The lecture was published only in a form of abstracted version entitled “Malignant Growth at the Cellular Level” (International Pathology, Volume 10, No. 1-2, 1969).

1 The present knowledge or general acceptance about the nature of the cancer cell (malignant cell) seems to lack in certainty in essential aspects which are beyond close examinations. Before entering into description of the observed transformation some of these aspects will be discussed.
for investigation in any aspect. Informations from studies with established cancer cells, however fine they may be, could not be sufficient for explanation of the sequence of changes taking place in the cell during the process of cancerization.

The problems of the earliest stage of cancer development, even though they are not subjects of real investigations, could not lightly be disregarded, since the important biological characteristics of cancer cells, which serve as guiding principles of cancer research, are acquired by the cell at this particular stage.

The author had occasions to discuss the problem of the earliest stage of cancer development in a lecture given at the University of Perugia (1961) [4] and later in the “Aschoff-Vorlesung” given in 1962 [5]. The discussion was based on the result of comparative studies on ascites hepatomas which indicated that every cancer cell originating in the liver of rats by feeding of azo compounds was individually different from each other. This individuality concept of cancer was presented earlier in 1957 in the Virchows Archiv in an article dedicated to Rössle on his 80th birthday [6].

II. Irreversibility of the Malignant Change

In the experiment of Yamagiwa, the histogenesis of the coal tar-induced skin carcinoma of a rabbit was thoroughly described from the very beginning of diffuse hyperplasia of the epidermal cells in the initial stage of coal tar painting up to the development of carcinoma. The initial diffuse hyperplasia was followed by papilloma (adenoma) formation, in which the carcinomatous change occurred, presenting histologically observable “malignant focus”, if it may be called as such. From this observation it was emphasized that mere continuation of the formative stimulation (after Virchow) on the cell, regardless of the nature of the stimulation, is sufficient to induce a malignant change, cancerization, at the end of a long continued “unspecific” cell proliferation.

Later, studies on the histogenesis of the azo dye-induced hepatoma of the rat confirmed the above-stated histological process of carcinoma development [6, 8]. The malignant change in this case was also observed within the area of the adenomatous hyperplasia that followed the diffuse hyperplasia, although this does not exclude other possible ways of malignant change of the cell, that is, malignant change without passing through the stage of adenoma formation.

In the whole history of the development of carcinoma described above, it is generally accepted that cell proliferation until adenoma formation depends on the external stimulation, that is, if the stimulus is removed at, or before, this stage the proliferation will come to cease. In other words, the process of cell growth during this period is “reversible” and, therefore, is regarded as “benign”. The growth, however, in the area which showed carcinomatous change, is independent of the external stimulation and continues its growth by itself. This “autonomous” growth is “irreversible” and is regarded as “malignant”.

It may, then, be rather natural that the unseen process of cancerization of the cell is realized vaguely by analogy with the whole serial pictures of carcinogenesis obtained by histological examinations in such a way that, at first, the stimulated cells repeat a pathological (but unspecified) multiplication by mitosis for a certain time; when this continuous process reaches a certain critical stage there occurs a “sudden” change in the cells; this change is discontinued from the sequence of preceding changes and a cell which underwent such a change acquires the characteristics attributed to the cancer cell, especially the ability of autonomous growth—the cancerization. The new characteristics of the cancerized cell acquired by this discontinuous change is irreversible and stable. The progressive pathological proliferation of the cells before final cancerization is reversible and benign, but the growth of the cancerized cell, which is discontinued from the host organism, is autonomous and malignant.

This is a theory of carcinogenesis which seems most prevalent, but this is certainly not a theory that was formulated or proposed by some individual. It must be regarded as a product of condensation of thinking of numerous pathologists who repeated observations of cancer development, and the idea of irreversibility or stability of cancer cells is widely accepted, even though one may be often unconscious of its influence.

III. Transformation of Sarcomatous Growth into Carcinomatous Growth

Since the establishment of Yoshida sarcoma in 1943 the origin of this tumor has been of great concern to the author. As stated in previous occasions, the original tumor was found as an ascitic growth in the peritoneal cavity of a rat in an experiment on inducing hepatoma by azo dye-feeding, and hepatoma nodules were present in the liver of this animal at its autopsy. Every tumor cell growing in the ascites, however, was individually separated without showing any sign of epithelial nature at all. The tumor cells infiltrated into the surrounding tissues, especially into the serotum, and formed an extensive solid growth. The histological picture of these solid tumors was sarcomatous, resembling the reticulum cell sarcoma.

Despite the presence of hepatoma nodules, from the point of view of pathology, there was no other way than to designate the tumor, both ascitic and solid growth, as sarcoma. The tumor was, thus, diagnosed as a reticulum cell sarcoma, supported by the following main findings: (1) The histological picture of the solid tumor formation was the closest to the generally accepted picture of the reticulum cell sarcoma, and (2) cytological examinations of the separate tumor cells in the ascites confirmed that they possessed almost all the cytological characteristics attributed to the so-called monocyte or isolated reticulum cell [9].

Of course, this process of diagnosis did not give any definite solution to problems either of the origin or of the mother cell of Yoshida sarcoma. Furthermore, two questions remained unanswered: Firstly, a successful induction of reticulum cell sarcoma by azo dye-feeding in the rat has never been reported. Secondly, an experience of spontaneous development of ascites tumor like Yoshida sarcoma in the rat has neither been reported.

Later, having seen the presence of the free-cell type of ascites hepatoma (see below), more firmly