CHAPTER 3

CANCER AS AN ORGANIZED CONDITION

IN THE CONCEPT now most widely accepted, cancer is considered to be the result of abnormal changes within cells. Although it is admitted that the disease may have different etiologies, it is the cell which is regarded as the pathogenic entity. A group of specific changes in the cells is believed to represent the fundamental abnormality.

In today's prevailing outlook, differences between tumors are attributed to the multiple secondary characteristics present in the diseased cells along with a primary specific anomaly. The complex clinical manifestations of cancer are further explained in terms of the relationship between cancerous cells, as pathogenic entities, and the whole organism. Clinical evolution, from local innocuous process to lethal disease is related to anatomical spread of cancerous cells from their original site. Abnormal metabolic changes seen in the organism are believed to result from the influence exerted by functional abnormalities of the cancerous cells. In a still narrower view, cancer is considered to be the result of abnormality of a single specific function of the cell—its growth. Qualitatively and quantitatively, abnormal growth has been considered to be the capital factor in the pathogenesis of the disease. (292)

In contrast to this classical view, our studies have led us to regard cancer as something other than an abnormality limited to the cell alone.

As we have seen, the organism is a complex hierarchic organization of different biological entities. We sought to determine where cancer fits in this complex organization. Can cancer with its manifestations and its evolution be better understood if systematized in accordance with the hierarchical organization of the organism? Can both manifestations and evolution be related not alone to a cellular abnormality but rather to a progressive par-

ticipation in the disease of the different hierarchic levels of the organism?

We have found that such participation cannot be analyzed readily in the advanced cancerous subject with so many and such varied manifestations of the disease already present. Similarly, incipient cases with a paucity of clinical manifestations are not ideal for the purpose. It was only by following the successive appearance of manifestations during the evolution of cancer that their relationship to the level of hierarchic organization involved could be clearly seen.

Identification of the level involved at each point in the development of cancer was greatly facilitated by conceptually separating the clinical evolution of the disease into a series of successive phases and identifying the changes which characterize the passage from one phase to the next.

We have chosen to call these phases precancerous, noninvasive, invasive, painful, preterminal and terminal. We will briefly identify them and their salient features here.

Precancerous Phase

In the precancerous phase, the disease is not clinically apparent. Yet this phase has been recognized as pathogenic in experimental carcinogenesis and its characteristic changes also have been identified in human subjects. Morphological changes—abnormalities in size and form—can be observed in the chromosomes. These changes are not identified as related to cancer in human subjects except where multiple centers of cancerization are found (as in the stomach, for instance). *(Note 1)* These chromosomal abnormalities can be considered to be precancerous lesions, since experimental carcinogenesis has indicated that these changes precede the appearance of cancerous cells. In terms of hierarchic organization, then, the precancerous phase can be considered to be limited to the subnuclear levels.

Noninvasive Phase

In the noninvasive phase, also known as "cancer-in-situ," abnormal intra-epithelial cells are present. The abnormality involves two changes. One, morphological, affects the nucleus; the other affects arrangement of the cells in the epithelium. The abnormal changes in the nucleus in this phase have been widely studied in exfoliative cytology. *(Note 2)*

Abnormality in this phase appears to be limited entirely to the nucleus. The cells continue to have an almost normally differentiated cytoplasm, a fact which originally led to the description of this phase as "cancer of differentiated cells." Besides the nuclear changes, cells in this phase show, histologically, an anarchic arrangement different from the regular disposi-

tion which is one of the basic characteristic of the epithelium. Since the regular relationship between the cells forming epithelium can be attributed to dipolarity, the anarchic disposition seen in this phase of cancer can be ascribed to loss of cellular dipolarity.

Cancer-in-situ, in terms of hierarchic organization, would appear to involve the level of the nuclei, and the noninvasiveness, characteristic of this phase, persists as long as the "cancerous" abnormality remains limited to this level, that is, as long as the cytoplasm of cells remains apparently unaffected.

Invasive Phase

This phase is characterized by irregular proliferation of cells and penetration into neighboring tissues. To the anarchic arrangements noted in the noninvasive phase, now has been added exaggerated growth. And the change of a noninvasive cancer into an invasive one can be considered to result solely from the addition of the new factor of abnormal growth. The invading cells will persist only if, concurrently, there is a loss of the defense mechanism of the invaded tissues, as will be seen later.

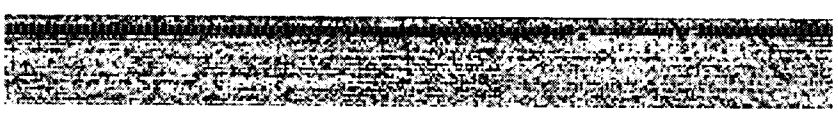
Studies of invading cells have revealed, in this phase, an anomaly no longer limited to the nucleus but now encompassing the cytoplasm as well. Exfoliative cytology has shown an abnormal and rapidly disintegrating cytoplasm and this has served as an important diagnostic criterion. From the point of view of organization, it can be said that, with the participation of the cytoplasm, the disease has progressed from the nuclear to the cellular level.

Painful Phase

Pain is the principal clinical manifestation characterizing the next phase of the disease. As we shall explain in greater detail later, pain arises from changes in the pH of the intercellular fluid that bathes sensorial nerve endings. For the moment, we can remark that biochemical changes now occur outside the cells, and, with the participation of interstitial formations, the disease has progressed to the tissular level.

Preterminal and Terminal Phases

In the next stage, the preterminal, biochemical changes affect the function of various organs which may or may not in themselves contain cancerous cells. While some changes in function may be seen even before this preterminal phase, now, there is manifest impairment. And, while the invasion of an organ by cancerous masses is a factor precipitating the func-



tional changes, invasion is not indispensable. Abnormal biochemical changes leading to serious functional impairments are seen in organs entirely exempt from tumor masses.

With further progress of cancer, metabolic functions that are systemically important become abnormal. Later, we will analyze in detail these changes which affect the whole organism profoundly. For the moment we want only to note that, with these changes cancer passes from the clinically preterminal to the *terminal phase*.

In the light of this systematization, cancer then appears to progress clinically in organized fashion as it passes from the relatively innocuous nuclear noninvasive cancer-in-situ to a lethal systemic disease, the progress being marked by the successive participation of different hierarchic levels of the organization. Table I sums this up.

TABLE I

Organizational Level	*Physiopathological Changes*	*Clinical Phase*
Subnuclear	Gene and chromosome anomalies	Precancerous
Nuclear	Nuclear anomalies and atypical cellular arrangements	Noninvasive cancer
Cellular	Atypical growth	Invasive cancer
Tissular	Local pH changes	Painful cancer
Organic	Organic metabolic changes	Preterminal cancer
Systemic	Systemic metabolic changes	Terminal cancer

By extrapolation, a similar progressive participation of hierarchic entities can be conceived of below morphologically recognizable levels. This would permit us, as a working hypothesis, to attribute the pathogenesis of cancer to abnormalities in nucleo-proteins or, even lower in the scale, to abnormalities in histones or alkaline amino acids. *(Note 3)*

This concept—of progressive participation of successive hierarchic levels in cancer—contrasts sharply with the view generally held today which places the entire burden of anomaly on the cancerous cell itself. The classical concept has led to the currently prevailing all-or-nothing approach in which therapeutic attempts are directed to the cancerous cells as the only avenue for controlling the disease at any moment of its evolution. Under our hierarchic concept, therapeutic possibilities can be extended beyond the cancerous cell.

These considerations raise the question of the relative importance of the multiple changes which occur in cancer. Subnuclear and nuclear changes are of relatively little importance as long as there is no progress of disease beyond these levels. Corroboration for this can be found in the great num-

ber of cases in which cancer-in-situ cells are noted in an organ, yet clinical cancer does not follow. In our concept, the changes which occur at levels above the nuclear are critical in the evolution of the disease and, as such, are the important pathogenic factors. On the other hand, as we shall see later, changes at higher levels similar to those encountered in cancer may occur independently of cancer, and without a sequence of changes at lower levels. It is only when changes at higher levels appear in proper sequence, affecting already abnormal entities of the lower levels, that clinical cancer results and the malignancy moves relentlessly from the noninvasive cancer-in-situ to the terminal phase.

This concept, then, focuses attention on all changes occurring at different hierarchic levels of the organization rather than on those in the cell alone. It emphasizes the importance of the relative independence which exists between the different hierarchic levels, an independence which governs their participation in the complex condition which is cancer.

From the therapeutic standpoint, then, it seems logical to suppose that, if the progressive participation of successive levels can be interrupted, many if not all of the noxious manifestations and the course of cancer can be favorably influenced. In view of this, it has been essential, first, to obtain more information about the cancer manifestations which are added as the disease takes its hierarchically progressive course and about the mechanisms that account for these manifestations.