Cancer, Retrodifferentiation, and the Myth of Faust

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Summary

The close relationship at the molecular level between cellular differentiation and neoplasia has been evidenced by the discovery in adult individuals of fetospecific antigens and fetal type isozymes associated with many spontaneous and experimentally induced malignant tumors. One question in relation with this finding is whether cancerous tumors develop from the differentiation of a tissue reserve of stem cells or by a process of retrodifferentiation, i.e., the nucleocytoplasmic stepwise reversion of cells toward stationary states with simplified structure and less information content. The question is not merely academic; elucidation of the nature of the target cells from which neoplastic growth emerges has obvious physiopathological and therapeutic implications.

This contribution is an analysis of the nature and the mechanism of cellular retrodifferentiation and a discussion of its possible role in regeneration and metaplasia, as well as in neoplastic development.

Throughout living systems, retrodifferentiation appears as a common adaptive process for the maintenance of cell integrity against deleterious agents of varied etiology (physical, chemical, and viral). While preserving the entire information encoded on its genome, cells undergoing retrodifferentiation lose morphological and functional complexity by virtue of a process of self-deletion of cytoplasmic structures and the transition to a more juvenile pattern of gene expression. This results in a progressive uniformization of originally distinct cell phenotypes and to a decrease of responsiveness to regulatory signals operational in adult cells. Retrodifferentiation is normally counterbalanced by a process of reontogeny that tends to restore the terminal phenotypes from where the reversion started. This explains why retrodifferentiation remains invariably associated to cell regeneration and tissue repair.

There is an ever growing evidence that neoplastic transformation in vivo and in vitro is frequently preceded and/or accompanied by biochemical, morphological, and behavioral transitions characteristic of a cell undergoing retrodifferentiation. Contrary to what occurs in regenerating tissues, the "unbalanced" character of tumor-associated retrodifferentiation seems to be a property linked to cancer. The question arises why a unique mechanism of cell rejuvenation is in physiological conditions (regeneration), followed by a process of reontogeny, while in neoplasia the process remains incomplete or does not occur and leads to the emergence of a populaton of persistently dividing cells.

It is to be hoped that a careful study of retrodifferentiation in physiological and tumoral models will help to distinguish that which in neoplastic development can be relevant to an adaptive cell behavior from that which might eventually be the result of specific or constitutive alterations.

Introduction

The bulk of information acquired during the past 12 years has provided evidence that numerous cellular constituents normally present during embryonic, fetal, or neonatal life, but absent or present at much lower concentrations in tissues and organs of mature individuals, reappear in neoplastic tissues. This and the resemblances observed between immature and cancerous cells at other levels of biological activity and structure have led to the conclusion that many spontaneous and experimentally induced malignant tumors converge toward stages of incomplete forms of cell differentiation.

There is an increasing awareness that differential gene expression is central not only to the problem of developmental and reparative growth but to that of neoplasia. While the arrest of cell differentiation has been advanced as a possible explanation of neoplastic development (25, 28, 36), the question that still must be answered is whether cancerous tumors develop from the differentiation of a tissue reserve of stem cells or after retrodifferentiation, the nucleocytoplasmic stepwise reversion of mature elements toward a more juvenile state. The question is not merely academic; elucidation of the nature of the target cells from which neoplastic growth emerges has obvious physiopathological and therapeutic implications.

The aim of this contribution is to outline current knowledge on the nature and the mechanism of cellular retrodifferentiation and to discuss its role in neoplastic development as well as in other processes, such as metaplasia and regeneration, which are closely related with the stability of cell differentiation. Some speculative considerations on its possible physiological significance are also presented that strongly suggest that retrodifferentiation is a unique property of living matter and a general adaptive process for cell integrity preservation against deleterious agents.

Differentiation versus Retrodifferentiation

The close relationship at the molecular level between cellular differentiation and neoplasia was revealed some years ago by the discovery of fetospecific antigens (1) and fetal type isozymes (31) associated with primary hepatomas in adult individuals. Their presence was later demonstrated...
in other malignant tumors [see reviews by Alexander (2),
Coggin and Anderson (11), and Uriel (37)]. Although cell
 constituents of this type are probably reexpressed in many
neoplastic cells, they cannot be considered as characteris-
tics of the malignant state, since such constituents may also
erange in adult tissues undergoing nonneoplastic growth.
The term "transitory cell antigens" has been proposed to
designate these normal biosynthetic products of the cellular
genome where expression is restricted to a transient period
of the overall process of cell differentiation (36). In mams,
certain types of these antigens appear only at the very
early cleavage stage of embryonic development. Others are
maximally synthesized around the middle of gestation, while
antigens like \( \alpha \)-fetoprotein are produced during rela-
tively long periods covering intrauterine and early postnatal
life. Another group is associated with the physiological
renewal of adult cells and tissues (e.g., the endodermal
epithelium, RBC and WBC, and germinal cells of the go-
nads). Transitory cell antigens and enzymes are, in fact,
widely represented during developmental cycles of most
living organisms, from sporulating bacteria (16) to mams,
including algae (34), insects (29), and amphibians
(10, 19).

One interesting property of these constituents is their role
as molecular markers of cell differentiation. Cell lineages
emerging in multicelled organisms from primordial ele-
ments diversify as development proceeds and become mor-
phologically and functionally distinct at the terminal stages
der differentiation. The precise delineation of the hundreds
of specific gene products along this intricately branched
family tree constitutes an impossible task. However, the
identification of transitory cell components, which are
much more limited in number, may provide a more accessi-
ble means of characterizing time phasing in developing cell
lineages.

Another central question relevant to the resumed synthe-
sis of fetal-type constituents in neoplasia lies in the general
problem of the reversibility of cell differentiation. A variety
of connotations, sometimes without clear definition, are
associated with the process of differentiation, whereas the
term "dedifferentiation" is even more loosely used to de-
scribe a loss of morphological properties in formerly recog-
nizable cell phenotypes. We shall consider differentiation as
a time and space sequence of metabolic and biosynthetic
patterns that reflect the diversified activity of the genome
during developmental growth and retrodifferentiation as a
sequence of nucleocytoplasmic events inverse to those of
differentiation.

This formulation was inferred from an analysis of the
dynamics of fetospecific antigens and isozymic patterns in
liver during ontogenic, compensatory, and neoplastic
growth (36). It postulates that differentiation and retrodif-
ferentiation are alternatives of 2 convergent directions of a
single chain of events and assumes that both directions are
potentially reversible. Thus, when an adult cell redifferenti-
ates or a stem cell differentiates, they probably travel
through similar stages of nucleocytoplasmic expression,
although sequenced in opposite order. Consequently, the
initial phase-specific transition in cells entering retrodif-
ferentiation should be similar to that of the terminal step of
their previous developmental history. For the same reason,
the synthesis of one or another immature antigen or enzyme
and, inversely, the loss of certain phenotypic structures and
molecular components would depend on how far the rever-
sion has proceeded (Chart 1).

As pointed out by Manes (23) "it is becoming clear that,
contrary to early assumptions, development does not in-
volve a gradual restriction of gene expression as ontogeny
proceeds from one phase to the next." Rather, the best
evidence yet available, although not abundant, indicates
that the metabolic and structural phenotypes of primordial
cells are sustained by relatively small portions of the ge-
nome. During the ontogenic phase, gene activation occurs
and specific cell structures, antigens, and enzymes are
produced, either transiently or permanently, in the somatic
cell lineages until differentiation terminates. By contrast, a
process of restrictive expression of genes specific to adult
phenotypes seems to characterize cellular retrodifferentia-
tion.

The question whether cell division precedes or follows
either differentiation or retrodifferentiation has not yet re-
ceived a conclusive answer. Both directions of growth are
probably characterized by alternate cycles of mitosis and
phasing of nucleocytoplasmic products.

Retrodifferentiation in Cell Injury and Tissue Repair

The irreversibility of the differentiated state has in the past
been a firmly held opinion and for many embryologists a
kind of indissoluble dogma associated with the concept of
differentiation. Yet there is no formal argument against the
assumption that retrodifferentiation is potentially inherent
in all somatic cells of an organism as long as their genetic
information content is preserved. In fact, experimental evi-
dence has accumulated in recent years that emphasizes the
central role of retrodifferentiation, particularly in regenera-

tive and neoplastic growth. The competence to revert may,

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Chart 1. Differentiation versus retrodifferentiation; alternatives of 2 con-
vergent and reversible directions of the same events. Cell lineages emerging
from primordial elements (x) diversify as development proceeds and become
morphologically and functionally mature at the terminal stages of differen-
tiation (A1, A2, D1, C1, D2, and B1). It is postulated that when cells rediffer-
entiate, they travel through similar patterns of nucleocytoplasmic expres-
sion, although sequenced in the reverse order to their own developmental
history. In regeneration, cells must revert through the corresponding path-
way up to the stationary state (i.e., D1 → d → c → b) from where redifferen-
tiation can start in the same (b → c → d → D1) or in another direction, the
latter leading to a metaplastic shift (i.e., b → B1). During preneoplastic
development, cells also retrodifferentiate but, at a given moment, the
process of compensatory redifferentiation remains incomplete or does not
occur and leads to the emergence of a population of malignant, persistently
dividing cells.

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however, vary in the broad range of cells of different organisms or from one cell species to another in the same individual.

An extreme case of reversibility of differentiation is illustrated by the experiments of Gurdon (15) with the nuclei from gut epithelial cells of Xenopus tadpoles. When nuclei from these differentiated cells were transplanted into enucleated unfertilized eggs of the same species, normal development into feeding tadpoles was promoted in some of the transplants. This experiment apparently implies the complete reversion of the nuclear genetic activity to a primordial stage before the reconstituted egg is able to resume the whole program of tadpole ontogenesis.

The epimorphic regeneration of resected parts of certain lower invertebrates has for many years attracted the attention of developmental biologists [see the review by Goss (13)]. There is now conclusive evidence that the blastema cells that accumulate at the site of transection of amphibian tadpole limbs emerge from retrodifferentiated mature elements, e.g., myocytes and chondrocytes (8, 17) and not, as formerly considered, from a reserve of undifferentiated stem cells. Moreover, there is a clear correlation between actual regeneration and the competence to retrodifferentiate. Thus, in nonregenerating limbs such as those of postmetamorphic anurans, amputation stimulates little or no retrodifferentiation, the damaged tissues at the amputated surface undergoing rapid individual healing. Nevertheless, when retrodifferentiation is forced to occur by prolonged injury to the stump, either mechanical (27) or chemical (30), regeneration follows. As Goss (13) has concluded, "... the principal disparity between regenerative and nonregenerative limbs may lie in their divergent capacity for dedifferentiation."

At the cellular level, retrodifferentiation results in the progressive disappearance of cytoplasmic structures characteristic of the mesodermic adult elements of the stump and their replacement by a simplified pattern of organelles common to many "undifferentiated" cells. It is this population of mesenchymatous cells that proliferate and form the regeneration blastema from which the different tissues of the limb will be reconstituted. Molecular events during the retrodifferentiation phase of limb regeneration are little known. The increased activity during this period of several hydrolytic enzymes including cathepsines, peptidases, collagenases, and acid phosphatases (33) probably reflects the marked predominance of autolytic processes. Of particular interest is the decrease in the glycogen content, which seems intimately related with the rise in aerobic glycolysis and the respiration rate observed during retrodifferentiation until blastema formation is completed. The high rate of lactate production attained at this moment gradually drops to normal adult values as regeneration progresses. Intensification of glycolysis under aerobic and anaerobic conditions is also associated with the embryonic state of most animal species, including man, and as will be seen later, with many cancerous tissues.

Another remarkable example of regenerative capability is provided by the Hydra. Under constant optimal conditions, this lower invertebrate bypasses sexual reproduction and regenerates entirely and continuously from a reserve of small basophilic cells, the so-called interstitial cells. However, it can also regenerate from practically any amputated part of the organism even when depleted of its population of interstitial cells by previous X-ray or nitrogen mustard treatment, to which these cells are particularly vulnerable. In such a case, regeneration occurs by retrodifferentiation and subsequent redifferentiation of preexisting distinct phenotypic elements. Morphological evidence of this mechanism resulted from the work of Burnet (9), who succeeded in promoting metamorphic regenerations of Hydra viridis after explants consisting of only gland cells and digestive cells were cultivated in appropriate media. The former reverted to the stage of interstitial cells which then divided and redifferentiated. The digestive cells transformed without apparent morphological signs of retrodifferentiation into epidermal cells.

Wolffian lens regeneration, which provides yet another example, is the unique property of certain kinds of urodel amphibians. After removal of the lens, the organ is completely regenerated by a cell population derived from the dorsal part of the iris epithelium. The fully differentiated iris cells convert into lens cells following an ordered stepwise sequence of morphological and biosynthetic patterns which starts by a retrodifferentiation pathway of the iris cells: nuclear activation, replication, and depigmentation. Afterwards, lens regeneration begins with the synthesis of lens-specific antigens (γ-crystallins) and progresses by morphological changes until complete lens organogenesis. The subject was recently reviewed by Yamada (39), who also pointed out that "... the convergence of regenerative and ontogenic lens formation implies that Wolffian lens regeneration involves recovery of an embryonic condition by the iris epithelial cell." This metaplastic change illustrates well the general assumption (Chart 1) that phenotypic changes follow strict requirements, ordered reversion toward a common ancestor, and then redifferentiation in another direction.

Liver regeneration of laboratory rodents, rats, and mice is probably the best investigated model of reparative growth in mammals and an excellent example of restricted retrodifferentiation without apparent metaplastic shifts. Although the cell-reverting phase of liver regeneration has been much less explored than the subsequent period of compensatory hypertrophy and hyperplasia, the data already available permit us to draw a general, although incomplete, picture. The process of hepatocyte retrodifferentiation in rats, starting immediately after partial hepatectomy, seems to be accomplished in no more than about 18 hr, the period that precedes the onset of DNA synthesis. At the cellular level, morphological alterations as summarized by Bresnick (6) consist of: (a) dispersion of cytoplasmic basophilic bodies; (b) disaggregation of endoplasmic reticulum; (c) decrease in the number of lipid bodies; (d) loss of stored glycogen; (e) simplification of the cell surface; (f) appearance of free ribosomes; and (g) increased lysosomal activity. Most of these morphological characteristics are coincidental with those of juvenile, i.e., fetal or neonatal hepatocytes and were also observed in hyperplastic nodules of rat hepatocytes appearing early in the preneoplastic phase of liver carcinogenesis by diethylnitrosamine (7).
Mayfeld and Bonner (24) have recently made an interesting study of early molecular events occurring before initiation of DNA synthesis in liver of partially hepatectomized rats. They were able to demonstrate as soon as 1 hr after the operation the sequenced production of rapidly labeled high-molecular-weight RNA and then of chromosomal RNA, both containing sequences not produced by normal adult liver. After 9 hr, a maximal 35% increase in the template activity of chromatin supported the conclusion of a significant derepression during this time interval of previously silent genes. According to Mayfeld and Bonner (24), these genes are presumably needed to prepare the cells for DNA synthesis and subsequent cell division. It is probable, however, that such nuclear activation also concerns genes involved in the synthesis of fetal-type antigens and isozymes that are observed during the 24- and 72-hr period of liver regeneration [see review by Uriel (37)].

This period induced in rats after partial hepatectomy or by the administration of hepatotoxic drugs has been the object of numerous studies and appears to be characterized by: (a) the increased synthesis of fetospecific liver proteins (α-fetoprotein, α2M-fetoprotein, lipoprotein esterase, cell surface antigens, etc.); (b) the transitory shift of some isozymes (glucose-ATP phosphotransferase, phosphofructokinase, pyruvate kinase, aldolase, etc.) to patterns relevant to immature hepatocytes; and (c) metabolic transitions leading to the predominance, as in fetal liver, of catabolic pathways over anabolic ones and a reverse behavior of protein and nucleic acid metabolism. All these temporary changes progressively vanish in about 2 to 3 weeks, while the morphological, metabolic, and nucleic properties of mature hepatocytes are recovered and the initial liver mass is restored thanks to cell division and enlargement. Last but not least, reversion of cell differentiation is frequently observed when normal cells and tissue explants are cultured in vitro. Metaplastic transitions, e.g., neuroblasts to melanophores, chondroblasts to fat cells, osteoblasts to chondrocytes, have also been reported. Auerberg and Finnegan (3), who have recently reviewed the subject, pointed out that the sequence of events, i.e., cell contact loss and migration, metaplastic transition, and proliferation, that follows tissue explantation into cultures resembles the process of wound healing. They also emphasized that the disturbance of the normal tissue architecture in tissue cultures always precedes retrodifferentiation. Then the subsequent loss of phenotypic properties progresses under the favorable effect of repeated cell divisions. Limited modulations in the differentiated state have nevertheless been observed when appropriate culturing conditions were tried, although most frequently the retention of permanent cell lines was coincidental with its neoplastic transformation.

The use of isolated liver parenchymal cells for in vitro cultures has been the object of intensive work during the last few years, and a multiauthor contribution on this topic has recently been published (12). Contrary to the results with fetal or neonatal hepatocytes, with hepatocytes from regenerating liver, or from established hepatomas, it has been difficult to obtain permanent cell lines from resting adult hepatocytes. Since mammalian adult liver possesses a high regenerating capability, this limited potential for in vitro proliferation is probably due to the lack of appropriate conditions to monitor the retrodifferentiation process in such highly specialized cells.

The evidence briefly outlined above permits the delineation of certain general traits of retrodifferentiation, a process that from lower to higher organisms appears to be widely represented throughout living systems. Thus, some kind of disturbance of the normal ecological equilibrium of cells and tissues seems to be an invariable requirement for promoting the process. Most frequently, retrodifferentiation initiates as a response to cell injury of varied etiology. The question whether the cells undergoing retrodifferentiation are those sublethally damaged or those situated in the vicinity of the traumatized area remains to be elucidated. Probably both kinds of elements participate in the process.

The ordered and progressive nature of retrodifferentiation that we have assumed seems to be sustained by several well-documented examples. The term dedifferentiation thus becomes inadequate, since it does not indistinctly qualify limited reversions such as the transition of adult to fetal type hepatocytes taking place in liver regeneration and the advanced level of retrodifferentiation of blastema cells from which tadpole limbs regenerate. Between these 2 extreme cases, intermediate levels of retrodifferentiation are provided by the varied phenotypes associated with several systems and particularly with neoplastic cells (see below).

Some common features of cells undergoing retrodifferentiation include a variable loss of cytoplasmic structure and complexity, the transition to a more juvenile pattern of gene expression evidenced by the synthesis of transitory cell antigens and enzymes, and the phase-specific restriction of genes characteristic of the mature state of each differentiated cell.

Retrodifferentiation is normally counterbalanced by a process or reontogenesis that tends to restore the terminal phenotypes from where the reversion phenomenon started. This redifferentiation may, in some circumstances, be the origin of metaplastic shifts leading to the appearance of mature elements distinct from those that initially retrodifferentiated. The acquired competence of retrodifferentiated cells for both regeneration or metaplasia appears to be narrowly dependent on the degree of nucleocytoplasmic reversion and of the developmental history of the cell lineages implicated in the process (Chart 1).

**Retrodifferentiation and Cell Information Content**

Living organisms are thermodynamically open systems that uninterruptedly exchange energy and matter with the external milieu. At any stationary state assumed by the organism, and as a result of internal and external factors, thermally labile structures and molecular cell components rich in information content are continuously broken down during a process of subcellular repair, designated as the "antifluctuation internal cell work" (35) which simultaneously operates to return the cell to its previous state. This mechanism is unique to living systems and vital to the maintenance of cell integrity at its stationary state. Deviations from this process beyond the "antifluctuation" capability of the system are extremely harmful and often lethal for the organism.
Contrary to metazoans, bacteria and other single-celled prokaryotes adapt quickly to changes in the external environment largely because of the plasticity of their mechanisms of genetic control. In multicelled organisms, however, additional processes have evolved to fulfill the new requirements provided by the increased complexity of the system, particularly the existence of a mosaic of specialized cells, each sustained by a differential pattern of gene activity. Efficient homeostatic controls, that assure the constancy of the internal milieu within narrow limits, provide a means of dampening anomalous fluctuations of internal or external origin. Retrodifferentiation seems to be an alternative to the cells' risk of undergoing irreversible deleterious changes when the homeostatic barriers are overpassed. It enables the cells to deviate temporarily, through adequate nucleocytoplasmic changes, toward stationary states better adapted to stressing environmental conditions.

The change is advantageous because, as far as we know, retrodifferentiation is a process of morphological and functional simplification, progressively tending to uniformize originally distinct cell phenotypes by virtue of a self-deletion of cytoplasmic structures and of cell information content that, consequently, leads the system to a level of higher thermodynamic probability and a lower dependency on environmental requirements.

On the other hand, while preserving the entire information encoded on its genome, the retrodifferentiated cell acquires increased competence to divide and to redifferentiate. If the reversion has proceeded far enough toward stationary states of greater immaturity, metaplastic transitions became possible (Chart 1). This explains why retrodifferentiation remains invariably associated with processes of regeneration and tissue repair.

Retrodifferentiation may be regarded as an adaptive process and, as such, would not be limited exclusively to multicellular organisms. Bacterial sporulation and the encystment phase of unicellular algae and protozoans resemble in many aspects retrodifferentiating transitions. Both are provoked by stressing environmental conditions and are characterized by: (a) the ordered inactivation of the vegetative genome and the switching on of specific genes as evidenced by the synthesis of new cellular components; (b) the loss and/or the simplification of phenotypic structures and metabolic functions; and (c) the potentially reversible nature of the change.

One general conclusion that can be derived from the above considerations is that retrodifferentiation, the self-reversible transition of a cell to stationary states of lesser structure and information content, appears as a unique property of living matter and a current adaptive process for the maintenance of life.

Retrodifferentiation in Cancer

The relationship between cancer and cell immaturity as determined from experimental findings was first formulated by Greenstein (14). From his own work and that of others, Greenstein concluded that "tumors tend to converge to common enzymatic patterns" that, in certain cases, resemble those of fetal tissues. The question was reinvestigated 20 years later. Since then, the increasing literature on the subject has emphasized the evolution of neoplastic development toward stages of incomplete forms of cell differentiation. The noncoincidental character of the transitions involved is now sustained by many conclusive observations.

Embryonic, fetal, and neonatal antigens have been found in numerous malignant tumors of diverse localization and etiology (spontaneous, viral, chemically induced, etc.). The great variety of cancerous tissues containing these types of antigens has evoked the possibility that most, if not all, tumor-associated antigens are related to transitional stages of cell differentiation occurring in the course of either intrauterine or extrauterine life.

The biochemical phenotypes of many tumors show analogous changes of reversion toward immaturity. The metabolic pathways and isozyme patterns characteristic of the functional activity of adult tissues tend to vanish when they enter malignant transformation and to be replaced by the rather common pathways and patterns proper to tissues undergoing developmental or regenerative growth [see reviews by Knox (21), Schapira (32), and Uriel (37)]. Therefore, when an isozymic pattern of a tissue differs from that of its fetal or neonatal counterpart (liver aldolase and glutaminase, kidney lactate dehydrogenase, etc.), the tumor expresses most frequently the fetal-type isozyme. The intensification of glycolysis, first revealed by the pioneer work of Warburg and his contemporaries, and the metabolic imbalance in close correlation with the growth rate, evidenced by recent studies of Weber (38), are widely common features of malignant tumors. The biological behavior of cancerous cells also frequently mimics those undergoing ontogenetic development: stepwise progression through division and differentiation cycles, low responsiveness to contact inhibition to replication, increased mobility and tendency to colonize and to invade resting neighboring tissues, agglutinability by plant lectins, etc.

Any of the immunological, biochemical, or behavioral traits outlined above are neither essential nor unique to cancer. Highly differentiated, slowly growing tumors may show morphological antigenic or biochemical patterns very close to those of normal resting tissues, and patterns of fetal or neonatal type can be observed in tissues undergoing regenerative or reparative growth.

The comparative analysis of fetal-type biological transitions accompanying hepatocarcinogenesis and liver regeneration led us to envisage them as demonstrative examples of retrodifferentiation in both neoplastic and normal mammalian tissues (36). Thus, while stepwise reversion toward immature cell phenotypes probably accounts for the antigenic and biochemical analogies observed between hepatomas and regenerating liver after partial hepatectomy or chemical injury, the dynamics of both processes are clearly distinct. In regenerating liver the change is a cyclic one. Initial retrodifferentiation of parenchymal cells is "counterbalanced" after a short period of active growth by a process of redifferentiation that restores the histotypic properties of the adult organ. During the preneoplastic phase of liver carcinogenesis, cells also retrodifferentiate, but at a given
moment and by an unknown mechanism, the system escapes compensatory redifferentiation and becomes malignant. Thus “unbalanced retrodifferentiation” may characterize neoplastic development arising, at least in adult tissues.

A somewhat different view was advanced by Pierce (25), who concluded from studies on murine testicular teratocarcinomas and on a malignant squamous carcinoma that, in carcinogenesis, the target cell is actually the stem cell normally present in tissues. It excludes adult or mature cells as possible targets for neoplastic transformation, since “what has been interpreted as dedifferentiation is, in reality, an abortive attempt of differentiation (26).”

The hypothetical presence of such a reserve of stem cells has, nevertheless, never been demonstrated in static or spanding cell populations (neurons, muscle cells, cells of the liver, kidney, connective tissue, etc.). In contrast, the limited, but significant, retrodifferentiation of adult hepatocytes before the 1st wave of mitosis following partial hepatectomy provides evidence that, at least in damaged liver parenchymal cells regenerate from rejuvenated adult elements.

An ever increasing number of cells with varied phenotypic characteristics can already be cultured as permanent lines and transformed by either physical, chemical, or viral agents [see reviews by Macpherson (22) and Auesperg and Finnegan (3)]. One can reasonably anticipate that, with increasing knowledge of the homeostatic and nutritional factors regulating cell growth and development, a greater number of cell types, whatever their level of differentiation, could be successfully maintained in long-term cultures and subjected to neoplastic transformation.

With respect to the question whether adult or stem cells are the target elements in carcinogenesis, the information already accumulated suggests that any cell at any stationary state along its differentiation pathway may provide the site where the initial events leading to cancer occur, however, the susceptibility to transformation probably varies for cells at different levels of differentiation.

There is also some evidence that malignant transformation in vitro is frequently accompanied by biochemical, morphological, or behavioral changes characteristic of cells undergoing retrodifferentiation. Thus, chick embryo cells transformed by strain MC29 avian leukemia virus have revealed, as compared with their normal cultured counterparts, a series of ultrastructural cytoplasmic alterations characteristic of immature cells (18) and resemble those responsible for the adult to fetal-type reversion of hepatocytes following partial hepatectomy (see above). Also, studies of a line of epithelial hepatoma-like cells transformed from a cultured line of normal epithelial liver cells (4) have shown transition to patterns of random multilayered growth, loss of responsiveness of growth restriction to high-cell densities and to intimate contact, alterations of the cell surface evidenced by the lessening of tight junctions, and the acquiring of cell agglutinability by plant lectins, among other traits associated with cell rejuvenation. Compared with normal controls, cells transformed by polyoma, SV40, and Rous sarcoma virus have been found to produce more lactate as a result of increased glycolysis, a property common to many rapidly growing embryonic, regenerating, and neoplastic tissues.

In summarizing this discussion, we wish to emphasize that (a) the so-called autonomy of cancerous cells, i.e., their lack or decrease of responsiveness to regulatory mechanisms operational in normal adult cells, may partly result from an adaptive process of life preservation against internal factors (aging, abnormal metabolism, and biosynthetic errors) or disturbing external agents; and (b) retrodifferentiation appears to be the most efficient mechanism underlying such an adaptive process.

The reversibility of the retrodifferentiated state in physiological conditions has been pointed out above. Although the “unbalanced” character of tumor-associated retrodifferentiation seems to be a property linked to cancer, this by no means signifies a definitive loss by the neoplastic cell of its potentiality to redifferentiate either in vivo or in vitro. Conclusive examples of the reconversion to the normal state are currently available [see review by Braun (5)]. Their rarity, however, attests to the high stability of the neoplastic transformation.

If the assumed role of retrodifferentiation is correct, then the question arises why a unique mechanism of cell rejuvenation in physiological conditions (i.e., regeneration) is followed by a process of reontogeny while in neoplasia, the process remains incomplete or does not occur and leads to the emergence of a population of persistently dividing cells. It is to be hoped that a careful study of retrodifferentiation in physiological and tumoral models will help to distinguish that which in neoplastic development is relevant to an adaptive cell behavior from that which might eventually be the result of specific or constitutive alterations.

Jacob (20) wanting to emphasize the powerful inheritance for life continuity among living organisms, wrote some years ago that “the dream of an amoeba is to become two ameobae.” Perhaps, “the dream of an ameba” is to escape death which would indicate that the same fears and the same desires haunt the living world from ameba to man. But if the ameba attains his immortality to a certain extent by alternating cycles of growth and division, human cells, like the cells of many multicellular organisms, are destined to die. It is tempting to say that for these cells neoplastic transformation is the only alternative against aging and death. Cancer may thus be regarded as the myth of Faust on the cellular level, the cells’ chimeric dream of rejuvenation and immortality, which, in the end, often turns into a fatal nightmare.

References
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NOVEMBER 1976
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*Cancer Res* 1976;36:4269-4275.

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