Carcinogenesis: A Facet of Living Processes*

HAROLD P. RUSCH
(The McArdle Memorial Laboratory, Medical School, University of Wisconsin, Madison 6, Wis.)

In 1937 the Surgeon General of the United States Public Health Service appointed a committee of leading scientists to "formulate, as far as possible, the fundamental aspects of the cancer problem and to suggest various lines of work which merit investigation." The report of this distinguished committee was published in 1938 (5). Some of their most pertinent conclusions were as follows:

1. The causes of cancer "are multiple and diverse and vary for each type of cancer."
2. "Once malignancy is established in a cell it becomes an automatic process, independent of the presence of a continuously acting agent of outside origin, and the new character of the cell becomes a fixed one which is passed unchanged to the descendants."
3. "The inherited state is an unstable or poorly balanced system confined to an organ or tissue in which the specific cells tend to become malignant either from functional strain or from unfavorable environmental conditions."
4. "Almost all, if not all, classes of cells may be rendered malignant under the influence of one or more agents."

Although no recent discoveries have invalidated the general conclusions reached 16 years ago, research during the intervening years has advanced at an ever increasing tempo, and it is only natural that some of the older beliefs would be clarified, others modified, and that sufficient evidence would be available for additional concepts. In this address, I shall point out how progress during the past few years in areas such as cellular physiology, genetics, and biochemistry has provided the framework for some new conclusions and interpretations. First, I would like to consider some of the mechanisms by which metabolic patterns can be altered.

INHERITED CELLULAR CHANGES

To keep pace with the rapid advances in cellular inheritance we must turn to fundamental experiments that were carried out with various forms of life without reference to the cancer problem. The geneticist, for example, has found that metabolic pathways are genetically determined. While it is impossible to cite all the references that support such conclusions, the line of research on mutations in Neurospora carried out by Beadle (6) and by Beadle and Tatum (7) illustrates this type of study. The finding that the mutant strains have their counterparts in many naturally occurring forms of life suggests the generality of the conclusions. From this work have come stimulating concepts of the origin of life and the idea that life is continually evolving (32, 46, 51).

It is a tempting leap to the assumption that each type of cell within the body of a higher animal represents a sort of mutant from some predecessor. With such an assumption the conversion of a normal cell to a cancer cell might simply be considered but another expression of the same process more clearly typified by the conversion of a streptomycin-sensitive strain of bacteria to a streptomycin-resistant strain. But these hypotheses still remain to be established. They are, however, becoming more amenable to testing in higher animals because of the manifold possibilities for studying the metabolism of tumors and nor-
ormal tissues by means of isotopic tracers, and such work forms a significant proportion of the present research at the McArdle Memorial Laboratory with which I have first-hand acquaintance (28, 40, 41, 59, 60). This concept of evolutionary change is applicable not only to the conversion of normal cells to cancer cells or to the individual stages in this process, but also to the conversion of drug-sensitive cancer cells to drug-resistant cancer cells. This process has been studied intensively in leukemic cells at the National Cancer Institute by Law (87), who has emphasized that the conversion is mainly a process of natural selection, in which a few resistant or dependent mutants survive and become the basis of a new line, while the sensitive cells are eliminated.

Ideas on the conversion of normal cells to cancer cells stem from the newer knowledge of how one cell type is transformed to another. Our ideas are at present in a state of ferment in this area, and we are witnessing great changes in some of our concepts of hereditary mechanisms. Where once we could deal only in terms of mutations of nuclear genes and the resultant Mendelian heredity, we now have at least four clear-cut extra-Mendelian mechanisms for changing the metabolic pattern of a cell. These are:

1. **Hereditary change by cytoplasmic segregation.**—This change is the result of the continued division of cells at a rate that outpaces the formation of cytoplasmic particles thus leading to the loss of such particles by simple dilution. Thus, those enzymes whose formation is controlled by these particles will be lost. Observations of this nature have been made by Sonneborn (62), Ephrussi (16, 17), Spiegelman (64), and others (34, 77).

2. **Partial hereditary transfer (genetic transduction) by desoxypentose nucleic acid (DNA).**—It is now widely accepted that the pneumococcus transforming principle is a specific type of DNA and that the introduction of this material into a receptor strain of bacteria induces one or more new heritable traits, presumably owing to the production of more of the same type of DNA (3). The phenomenon has been extended to other transformations (33).

3. **Partial hereditary transfer (genetic transduction) by viruses.**—The most recent of the extra-Mendelian mechanisms has startling implications if the phenomenon can be extended to mammalian cells. It has been found that bacteriophage grown in one strain of bacteria can infect another strain without killing it, and, in so doing, can carry with it (or transduce) a new metabolic property into the new host (38). In all experiments thus far, only one property could be transduced at a time, but, by successive transductions, as many as five new metabolic characters or reactions could be introduced into and retained by a strain that originally lacked all five of them, thus converting it into five strains. This mechanism may be intrinsically similar to the one described under point 2 if the genetic fragments carried by the bacteriophage were considered to be DNA.

4. **Hereditary change by the establishment of lysogeny.**—Freeman and Morse (19) demonstrated that an avirulent culture of a diphtheria bacillus could be changed to a virulent one from a symbiote infection with a bacteriophage. In lysogeny the phage *per se* produces the heritable alteration in contrast to transduction, whereby the phage merely acts as the carrier of genetic material from one cell to another.

**CARCINOGENESIS**

With all these possibilities of cellular change, it is clear that studies on the problem of carcinogenesis have ample inspiration. Any or all of the above mechanisms could be concerned in the conversion of normal cells to cancer cells, and cancer investigators are deeply indebted to the biologists who discovered these interesting mechanisms. We shall now examine the evidence which indicates that similar mechanisms are involved in carcinogenesis, but first it is necessary to emphasize that the development of cancer is far more complex than the transformations observed in the unicellular organisms. A pure strain of cells living under controlled conditions is not subject to the action of antibodies, fibroblasts, leukocytes, hormones, and other factors that help to regulate life in multicellular organisms. Thus, it is to be expected that the changes leading to cancer will be complicated and extended because of the moderating influence of the host in combating deviations from the norm. Despite these complications we have reached the stage where it is not premature to examine the biological and biochemical evidence which indicates a similarity in the processes that result in heritable cellular changes in unicellular organisms and in cancer.

*First*, there is some indirect evidence that the cause of some cancers is associated with mutations of nuclear genes. Such evidence is based on the findings that nuclear changes are associated with cancer, that carcinogens cause chromosomal aberrations (26), and on the corollary finding that some carcinogens are mutagenic and some mutagens are carcinogenic (2, 29, 30, 36).

*Second*, carcinogenesis may result from dele-
tions of cytoplasmic factors in a manner analogous
that observed by Ephrussi in yeast transformations (16, 17). In the McArdle Memorial Laboratory, James and Elizabeth Miller (44, 45) have obtained evidence compatible with this view. They have demonstrated that the carcinogenic amino azo dyes form firm complexes with normally occurring proteins of the liver; but no similar binding was found in hepatic neoplasms. Their results suggest that the carcinogen causes a gradual deletion of certain proteins that are necessary for specialized features of the cell but not for the growth pattern. Similar complexes between proteins of the skin of mice and carcinogenic hydrocarbons have also been demonstrated by E. C. Miller (48) and by Heidelberger (72–74). Of special significance is the fact that carcinogenic activity of compounds tested is correlated with the amount or rate of binding (44, 45). Collaborative experiments by Potter, Price, Miller, and Miller (50) have demonstrated pronounced progressive decreases in certain cytoplasmic enzymes during carcinogenesis in the case of rat liver.

Third, if nucleic acids or nucleoproteins as pure chemical entities or in a form carried by viruses can be passed from one strain of cells to another and thereby induce or transduce heritable alterations in the metabolic pattern in bacteria, one must inquire whether similar phenomena occur in some types of carcinogenesis. At present we have only the cases in which viruses have been shown to convert normal cells to cancer cells (10, 53, 54, 61), and it is not clear whether the process is analogous to transduction or lysogeny or whether the introduction of the virus leads to a cytoplasmic deletion by competitive interaction. It appears probable that the viruses act at the cytoplasmic level and that their action is not strictly analogous to the DNA transformations which evidently act at the nuclear level.

It is of interest to recall at this time that a phenomenon similar to transduction or lysogeny was foreshadowed and illustrated by the pioneer work of Peyton Rous and his associates (53) when they demonstrated that a cell-free extract of an osteochondrosarcoma could “transduce” connective tissues in voluntary muscle into osteochondrosarcomas. The implication of this finding was not lost to them, since in 1913 they stated (55), “It is very remarkable that such an agent should bring about a differentiation ordinarily foreign to the tissue.”

The solution of carcinogenesis would be complicated enough if a thorough understanding of the mechanisms of inheritable cellular changes were the only aspect of the problem requiring clarification. We now recognize that the formation and growth of some tumors are prolonged processes, in some types involving three or more separate periods: (1) the stage in which an inheritable cellular change occurs (called the period of initiation), (2) the period called promotion in which the altered cells proliferate and become an autonomous cluster, and (3) the period during which the autonomous mass invades and metastasizes. Usually it is not until this last stage that cancer is clinically recognizable. The three periods are illustrated in the experiment in which tumors are initiated in the skin of mice by a single application of a carcinogenic hydrocarbon and promoted to an autonomous cluster of cells by the frequent applications of croton oil (9, 56, 57). The autonomous mass then grows and invades the adjacent tissues in the absence of inciting agents. Other examples of the prolonged process of cancer formation are presented in papers by Blum (11), Furth (21), and Gardner (24).

On the basis of hundreds of experiments on the subject of cancer and ancillary fields, it is now possible to present a simplified diagrammatic picture of the factors which control the reduplication and specialization of cells and to indicate how this normal pattern can be altered during the formation and subsequent growth of neoplasms. Although the concept to be presented takes root from such facts, it must be admitted that it is partly speculative, and I am not, and hope you will not be, deluded with the belief that the picture is complete or perfect. I would be pleased, however, if it would suggest further experimentation, since that is the real reason for presenting it. I would like to begin with a discussion of normal growth and differentiation.

NORMAL GROWTH

For the purposes of the present discussion all cellular functions are divided into two chief categories: one, the function of reduplication, and two, all other special functions not primarily concerned with cellular multiplication. The following discussion is based on the concept that the process of cell reduplication and the special functions interact in two distinct ways. In addition to being mutually dependent, the various functions must also be recognized as mutually competitive with respect to the cellular nutrients required for their synthesis. Thus, the development of cells is a resultant of the outcome of the dynamic balance between the functions of cell reduplication and of special function.

Chart 1 is a diagrammatic representation of an unfertilized ovum containing symbols which represent these two chief cellular functions together.
with the cell food necessary for such activity. This representation has been reduced to the very simplest terms. Potential mechanisms for cellular reduplication are represented by a hollow square and potential mechanisms for specialized cellular functions are shown by hollow circles. The numerous specialized functions of the cell have been reduced to four, each represented by a circle, which may represent a single enzymatic reaction or a series of integrated metabolic processes; but, since cellular reduplication is basically similar in all cells, only one square is used. The short straight bars arranged at random at one side of the cell represent the cell food or nutrients, also frequently referred to in the literature as building blocks, precursors, or substrates. While it is tempting to indicate whether the various mechanisms are nuclear or cytoplasmic, no implications are here intended.

The term cellular reduplication is preferred, because there can be no mistake about its meaning; but to reduce monotony the terms cellular division, proliferation, and “growth” are also used. Growth is the least desirable term because of its broad meaning, but it has the advantage of brevity.

The second chart illustrates the sequence of events which is associated with the “growth” and differentiation of normal cells. Cells with the most specialized functions are shown at the right, and the immature ones are at the left. The arrows within the cells represent the concepts of dependence and of competition. The arrows between the cells represent many stages and cells in transition.

In this diagram, cell A represents the toti-potential fertilized ovum. Immediately following fertilization, the mechanisms for reduplication and for special functions become activated, and this is indicated by the arrows from the cell food to the functions. Both mechanisms have increased in size. The first special system to become functional is the one represented by the circle labeled F. As the products of its reactions become quantitatively significant, some of these metabolites are used
to catalyze and initiate the next sequence of reactions as depicted by the arrows labeled 1 and 2. The ultimate characteristics of the differentiated cells are predetermined by the particular system of reactions which is nurtured in the first few generations of cells. If, in a given cell, the H function is the first one to be stimulated, as indicated by arrow 1, the subsequent course of events in descendents of this cell will follow the upper sequence of events culminating in cell E. If the special function s is the first to be activated, as shown by arrow 2, the end results are represented by cell E.

The course of events associated with the normal growth and differentiation of the mature cell will be described first. This is the bottom row of cells.

Cell B represents the primordial cell which is destined to develop into specialized mature cell E. Please note that the first specialized function, marked by r in the fertilized ovum, has disappeared during the many stages between cells A and B. The products of the reactions of the special function s, have by this time attained sufficient proportions to trigger and sustain the next sequence of events, function L, and to provide energy and metabolites for other intra and extracellular functions. This flow of metabolites from circle s is indicated by arrows. The utilization of cell food from the general pool by the mechanisms of reduplication and specialized functions at this stage is shown by the heavier arrows.

Cell C represents a further development, as indicated by the increased size of the special function L. Besides contributing its own distinctive attributes to the cell this function in turn stimulates the third function, H, and may feed metabolites back into the general pool of cell food. This stage clearly represents how one reaction activates a second, and the second starts a third, and so on; thus, a series of mutually dependent endogenously induced enzyme formations lead to an orderly sequential development of differentiation. Without such provision, growth and maturation would be chaotic. This mechanism for sequential development is not idle speculation, but is based on the fact that a number of interlocking metabolic reactions have already been shown to initiate and sustain secondary chemical reactions in this manner (42, 49, 52, 75). It is also based on the observation that some enzyme-forming systems in unicellular organisms can be stimulated to produce the enzyme for a substrate by the introduction or accumulation of suitable levels of the given substrate, thereby producing profound changes in the metabolic patterns of a cell without altering its hereditary makeup (32, 66). This phenomenon was formerly referred to as adaptive enzyme formation but is now known as induced enzyme formation (14).

Only meager evidence for the occurrence of induced enzyme formation in higher organisms exists. For example, Knox (35) has found that the tryptophan peroxidase activity of mammalian liver increased many-fold in response to injections of large amounts of tryptophan. For a variety of reasons he considers this effect due to an increase in the actual quantity of this enzyme. It might be anticipated that the loss of any given enzyme at a particular stage of differentiation or carcinogenesis would lead to the accumulation of the substrate for that enzyme. By the mechanisms of enzyme induction, such an accumulation could then facilitate the increase of enzymes for alternative pathways previously present in lower amounts.

From this schema we may obtain clues concerning the late manifestations of certain inherited defects. The explanation for some of these imperfections appears intelligible if we consider that the responsible defective function is one of the last induced systems to unfold in the developmental process.

The next stage (cell D) illustrates several interesting changes; the activity of the last special function, labeled H, has reached significant proportions, while the reactions of function s have decreased to an extent where they no longer influence the metabolic pattern of the cell, as shown by an absence of the arrow. This cell is a functional one, and the mechanism for reduplication, while still present, is no longer effectively competing for cell food, as indicated by the absence of an arrow from the precursors to the small square. At this stage the cell may retrace its steps during the process of reduplication or it may continue on its path to final irreversible maturation and death. The path to the irreversible stage is shown by an arrow leading to cell E. This cell has lost its potentiality to reduplicate (note the absence of the square), and all the precursors are funneled into the special functions of the cell. Any mature cell which is no longer capable of multiplication is representative of this stage. Thus, the course of events leading to differentiation is pictured as the sequential deletion or segregation of some metabolic patterns and the concomitant activation or induction of other systems. Similar suggestions have been made by several investigators (17, 65, 70, 71, 76). Such deletions are represented by the absence from cell E of function s. The concurrent increase in the remaining special functions is depicted by the enormous size of function H.

If the path to be followed is reduplication, the
course of events is in the opposite direction from that depicted for irreversible maturation. Cell D represents a mature cell with a potential capacity for reduplication, but in order to divide it must first retrace some of the processes that led to its maturation. The mechanism for reduplication might be described as follows: When a cell divides, the mechanisms for special functions and reduplication are diluted in the daughter cells and must be gradually rebuilt. For some unknown reason the patterns for specialization recover most rapidly, but the mechanism for growth also recovers, although at a slower pace. As the growth mechanism slowly gains ascendancy, the special functions disappear in the reverse order in which they appeared; function H becomes inactive before function L, and so on. Eventually the processes for reduplication become dominant and utilize an ever-increasing share of the cell food until a time is reached when the specialized systems no longer play a dominant role in the over-all metabolism of the cell. At this time mitosis begins.

Cell E' represents an irreversibly mature cell of a different type than cell E. The sequence of events controlling its growth and differentiation is similar to that just described. The chief difference is that it acquires some special characteristic metabolic patterns which differ from those in cell E and retains some features identical with those in cell E. This is shown by the dominance of function S in cell E' and function H in cell E. The L system is common to both cells.

At this time, let us momentarily retrace our steps to the earliest stages in embryonic development. During this period some cells along the path A-B' "induce" differentiation in cells along the path A-B (31, 63). The mechanism of induction might be similar to the orderly and synchronous development of the metabolic patterns just described except that the inducing substances originate in neighboring cells.

It should be stressed that the competitive pathways leading to reduplication or differentiation are in delicate equilibrium; only slight shifts are required to divert them one way or the other. Cell reduplication could be stimulated by any process that diverts the cell food to the growth pattern. One way to accomplish this is to inhibit one or more of the special functions. Perhaps estrogenic hormones and croton oil stimulate mitosis in this manner. If excessive demands are made on the special functions, cell division would be retarded and hypertrophy result, whereas factors harmful to special functions would stimulate growth and result in hyperplasia.

On the basis of the evidence which engendered the diagrammatic scheme just presented, I would like to offer the following statements as a concept of normal growth:

1. Normal primordial cells contain many potential mechanisms which ultimately determine differentiation. These mechanisms become functionally active when the constituents attain certain quantitative levels.

2. During the process of growth and differentiation, each living cell acquires or maintains certain biochemical processes or metabolic patterns in common, but in addition each cell type has special characteristic deviations from the general pattern, resulting from variations in its enzyme makeup.

3. The specific cell pattern results from the deletion of some of the original complement of mechanisms and from the concomitant increase in other functions. These losses and increases occur in a sequence which serves a useful function and is beneficial to the general economy of the organism.

4. In normal cells the competing processes for reduplication and for special function alternate in dominance until the final stage of maturation is reached. Then the pattern for reduplication is irrevocably lost in some cells.

THEORY OF CANCER FORMATION

I would now like to consider some aspects of carcinogenesis. In the beginning I referred to some of the conclusions concerning the nature of cancer made by the committee in 1938. Two of the conclusions were that the causes of cancer "are multiple and diverse" and that "once malignancy is established in a cell it becomes an automatic process . . . which is passed unchanged to the descendants." Research during the intervening years has sustained this report, and, in addition, sufficient information has been accumulated to indicate that all carcinogens induce heritable cellular changes.

This change is depicted in the alteration of the normal cells B, C, and D to the neoplastic cells U, V, and W as shown in Chart 3. To save space, the normal course of events (B' to E') in the development of one type of differentiated cell has been omitted. At first glance little difference is noted between the patterns in the various cells in the top two rows; both have the same complement of cell food, and both possess considerable specialized function. But one crucial difference exists. A key reaction in one of the special metabolic patterns has been irrevocably lost—a defect which is heritable. This is indicated by the large cross-covering the involved system. As will be described later,
some ancillary reactions of the altered pattern may persist temporarily, and these are indicated by the short arrows pointing away from the crossed circles. The initial alteration may be either nuclear or cytoplasmic in origin.

Although the heritable alterations in cells U, V, and W affect some specialized function, it will be noted that a different function is altered in each cell depicted. On closer scrutiny it is evident that the future course of the cells is determined by the particular system which has been altered. If the many of the other specialized functions will be secondarily disturbed. Such a cell is potentially capable of forming a very anaplastic neoplasm. Since each cell has a large complement of many special functions, it becomes obvious that almost any variation of cell type is possible. Indeed, it is fortuitous that any two tumors should be exactly alike when one considers the variety of combinations that could result when one or more functions are altered simultaneously or sequentially. Defects in special functions may be induced by carcinogens in any stage of normal development such as cells B, C, D, or E, but neoplastic cells can never result from cell E because there is no mechanism for transmitting the change.

It is also obvious that carcinogens produce a variety of biochemical lesions which are not heritable. The cell may recover from some of these lesions and succumb to others. Some of the initial changes produced by carcinogens may not differ from lesions from other toxic agents; the chief difference is that carcinogens can also induce heritable alterations.

While it appears possible that the altered cells U, V, and W may arise from any one of the stages...
of normal cells B, C, and D, it is probable that
cell U is more likely to arise from cell D than from
cell B and cell W is more apt to arise from cell B
than from cell D. Some, but not all, of the path-
ways from the normal to the defective cell are
indicated by arrows made of dash lines. A se-
quency of such arrows depicts a series of many cells
and stages rather than a single change. The period
of transition from the normal cells B, C, and D
to the altered ones U, V, and W corresponds to
the period of initiation as defined by Rous (20)
and others (8). The horizontal lines which break
the dash lines indicate the time when the revers-
ible condition passes into an irreversible one.
That the process of initiation may be reversible
for a period is demonstrated by the fact that cer-
tain carcinogens must be administered for a con-
siderable time before neoplasms result (13, 58).

Although each cell represented by U, V, and W
has a heritable loss of one specialized function and
is therefore capable of giving rise to a neoplasm,
the conversion into an autonomous cluster of cells
does not always proceed rapidly. The cell still re-
tains a considerable amount of extraneous but
competitive cellular constituents which were a part
of the once active special system. Such con-
situents must disappear before the final conver-
sion is complete. The removal of such substances
is by a gradual deletion usually occurring with
each cell division and culminating in the change
of cells U, V, and W to X, Y, and Z, respectively.
This change is depicted by the absence from cells
X, Y, and Z of the specialized functions marked
with the crosses in cells U, V, and W. The final con-
version just described corresponds to the period
of promotion as described by Rous (20) and others
(8), and the series of changes during this period
are shown by the arrows made of the long dash
lines. The specialized systems, h in cell V and l
and n in cell W, which were directly dependent on
the products of the inactivated precursor reac-
tions, are not shown in cells Y and Z. It must be
remembered, however, that some specialized sys-
tems may be functioning at very low levels. It is
obvious that many variations are possible in this
schema, but that cell Z represents the ultimate
degree of anaplasia. In the benign tumor (cell X)
the arrows indicate a reactivation of function s at
a level comparable to that seen in normal cell C.
Such activation is possible because of the reoriented
equilibrium of the cellular systems following the
loss of one or more of the other functions.

Some neoplastic cells may lie relatively qui-
escent for long periods without losing their ca-
cacity to be promoted. This is illustrated by epider-
dermal and testicular tumors which may be pro-
moted with croton oil (9, 56, 57) and estrogen (23),
respectively, 1 year after the initiation of the tu-
or. Similarly, the hormonally dependent tumors
as studied by Furth (21) and Gardner (24) also
require a considerable period for initiation and
promotion to the neoplastic state.

Cells intermediate in malignancy (cells X and
Y) may suffer a further loss of specialized function
and pass to the next lower level. The continued
deletion of special characteristics from neoplastic
cells through successive cell generations has been
clearly demonstrated by various investigators
who have studied the genetic factors required for
successful transplantation of neoplasms (4, 25,
27). Such studies demonstrate that tumor cells,
once incapable of growth in homologous strains,
may after prolonged growth be successfully trans-
planted to previously resistant hosts. This indi-
cates that the number of histocompatibility genes
required for successful transplantation may be
progressively lost from the growing cancer cell
(25). This process is probably to be identified with
the term progression as used by Foulds for de-
scribing the changes of neoplastic cells to the more
malignant state (18).

Cell Z represents the most advanced stage of
anaplasia. Such a cell has lost its major potential
for specialized function and it is doomed to a con-
tinuous process of reduplication. It represents a
reversion to a unicellular type of life. This ad-
vanced stage seldom if ever results in an animal
bearing a spontaneous or induced cancer, because
the host does not live sufficiently long to permit a
complete regression, but such neoplastic cells are
illustrated by certain types of ascites tumor cells
derived from tumors which have undergone re-
peated transfer. The tendency for unicellularity
is evident to a lesser degree in all neoplasms which
tend to form abnormal architectural patterns and
give rise to cells which metastasize.

On the basis of the discussion just presented we
may extend the conclusions reached by the com-
mittee 16 years ago with the following ideas:

1. Carcinogens induce a change in one or
more of the special functions of the cell. The
resulting change is heritable.

2. An untimely alteration of function dis-
rupts the normal sequence of differen-
tiation and the resulting metabolic patterns. In
such cells, the pattern for reduplication is
retained and predominates to varying degrees.

3. Cells which have suffered from such herit-
able change may require the additional loss of
accessory factors before becoming completely
autonomous neoplasms.

4. The formation and growth of cancer cells
are affected by conditions within the host—the genetic constitution, the hormone balance, the diet, the presence of irritation, chemotherapeutic agents—any factor that affects the internal environment of the host.

It appears clear from the above points that the causes of cancer may be varied and multiple and that the point of initiation may be nuclear or cytoplasmic. Just as the causes may be multiple it is clear that the metabolic patterns of neoplasms may include a diversity of features from normal cells.

COURSE OF ACTION

I am fully aware that the concepts just presented are far from complete, and, at best, can only emphasize weaknesses in our present knowledge and help to provide the framework for the design of further experiments. Before concluding, it may be appropriate to emphasize a few of the approaches that are worthy of further consideration.

First, in searching for the causes of cancer and their eventual elimination it is well to consider the dual roles of initiation and promotion as causal mechanisms in the formation of some types of cancer. Not only must we clarify our understanding of the mechanisms by which carcinogens produce heritable changes, but we must also investigate the methods by which these processes may be modified. For example, hormones (21, 24), caloric restriction (18, 67), and irritation influence tumor formation, yet too few investigators are searching for new agents to block hormones, for methods to neutralize the favorable influence of caloric excesses on carcinogenesis, and for means to combat the more subtle types of irritation.

Second, we must seek further information about the metabolic patterns which characterize cellular reduplication and specialization. The step-by-step mapping of the individual reactions of many alternative pathways forms a large part of the research program at the McArdle Memorial Laboratory (28, 39, 41, 47, 48, 59, 60, 68, 69). In this work the eventual localization of the sites of action of antigrowth agents is one of the important goals. This knowledge is required as a firm foundation for the chemotherapy of neoplastic diseases and helps to orient our thoughts about the various approaches to therapy. One possibility is to divert cell food from the growth pattern by increasing the level of some quiescent special function. Another would be to supply artificial substrates to the malignant growth process in order to obtain a defective growth mechanism in the cancer cells.

Third, a more thorough investigation of the phenomena of invasion and metastasis deserves greater emphasis as another approach to therapy. Additional information is needed concerning the role of fibroblasts, leukocytes, and enzymes in limiting or enhancing invasion and metastases. The experiments of Algire (1), Coman (15), and others provide stimulating leads. Further work in this direction may lead to a definitive experiment that will permit us to understand how the invading cell evokes a favorable vascular response and overcomes the forces that prevent growing tissues from overstepping the boundaries that are compatible with the best interest of the host.

Finally, since neoplasms in humans usually retain certain specialized features of the mature cell, the response of such tumors to therapy must depend to a considerable extent on the amount of the retained characteristics. Therefore, no chemotherapy screening program should depend entirely on animal tumors which have suffered a considerable loss of special functions through repeated transplantation.

CONCLUSION

In closing, it seems important to emphasize that the attack on the cancer problem is a fine example of a research effort in which the various branches of biological science cooperate in a common cause and in which the old departmental classifications no longer apply in a strict sense. The modern investigator of malignant growth frequently brings to bear not only the disciplines of physiology and biochemistry, but also the specialties of genetics, embryology, bacteriology, pathology, virology, and many others, which stimulate and nurture one another.

The concept of carcinogenesis presented in this report was based on facts which have emerged from numerous seemingly unrelated investigations in these various fields. Such concepts are worth while only if they engender additional advances, since each advance is dependent on some prior gain made elsewhere, and each advance, from the preliminary spadework to the completed harvest, stimulates and catalyzes new advances. Thus, haltingly but relentlessly, step by step, we continually improve our knowledge of the problems confronting us.

The report by the committee published in 1938 ended, and this talk will end, with a statement with which we can all agree, "In any program for cancer research, patience and, the adoption of a long-time point of view are absolutely essential."
REFERENCES


Downloaded from cancerres.aacrjournals.org on November 7, 2017. © 1954 American Association for Cancer Research.
73. ———. The Interaction of Carcinogenic Hydrocarbons with Tissue Constituents. II. 1,2,5,6-Dibenzanthracene-9,10-C14 in Skin. Ibid., pp. 250–54.
74. ———. The Interaction of Carcinogenic Hydrocarbons with Tissue Constituents. III. 1,2,5,6-Dibenzanthracene-9,10-C14 in the Submaxillary Gland. Ibid., pp. 255–61, 1953.
Carcinogenesis: A Facet of Living Processes

Harold P. Rusch


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/14/6/407.citation

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.