By the term “mitotic cycle” is meant the series of events which occur from the inception of one mitosis to the inception of the ensuing one. For purposes of discussion, this cycle may be divided into 4 segments; namely, active mitosis, synthetic stage, resting phase, and antephase. The relative durations of these segments is, for the most part, unknown and probably varies depending on a variety of factors such as age, metabolic state of tissue, etc. Furthermore, the transition between stages can scarcely be considered as being abrupt. Nonetheless, the segments of the cycle mentioned above must represent somewhat different levels of physiological activity. Despite the lack of detailed information concerning the more important changes which occur during the mitotic cycle, it is still possible to set up a general model which at least has value as a basis for experimentation. The diagrams in figures 1A and 1B represent two such models (1A for the multicellular organism; 1B for the unicellular organism). This paper will be concerned largely with some of the major questions which consideration of these two models inevitably raises.

The 4 segments of the mitotic cycle may be defined as follows:

1. Active mitosis. This stage represents that part of the cycle during which active division of the nucleus into two daughter nuclei occurs.

2. Synthetic stage. By this stage is meant that period following active mitosis during which major growth of daughter cells occurs. This stage obviously involves considerable synthetic activity, since the daughter cells must increase by a factor of approximately two in size.

3. Resting phase. This stage is a somewhat hypothetical, but obviously necessary, stage between the end of synthesis and the regaining of high mitotic competence. This is presumably a stage of comparative quiescence and would seem to be the period during which a cell would be most likely to undergo differentiation under appropriate conditions (see figures 1A and 1B.)

4. Antephase. This term has been used by Bullough (1952) and also by Wilson and Hyyppio (1954) to designate a stage just prior to the inception of active mitosis. The major morphological criterion for such a stage is a

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characteristic increase in the volume of the nucleus. Although numerous other changes must also occur, these are less well-defined at the present time.

Fig. 1. Diagrammatic representation of the Mitotic Cycle. A, in multicellular organisms. B, in unicellular organisms.
It is obvious that a cell in a single revolution of the cycle must perform a whole range of functions and must be in a constant state of physiological change. Irrespective of the actual energy relations involved, one is justified, at least, in making the generalization that the cell passes from one physiological level, through a range, and back to its original level. In deciding how this may be accomplished one might make certain assumptions concerning the energetics involved in each of the individual segments of the cycle. We might assume, for example, that the energy requirements for active mitosis are met through glycolytic activity while those for synthetic activity are met through operation of the Krebs or tricarboxylic acid cycle. Both of these assumptions are compatible with our present state of knowledge regarding cell division (Brachet 1957, Hughes 1952, Stern 1955, Wilson and Morrison 1958.) The operation of the entire mitotic cycle may then be explained on the basis of a series of shifts in balance between these two energy-producing systems. It is, therefore, not unlikely that certain segments of the cycle are characterized by higher activity of one or another of the two systems. The resting stage is probably intermediate in this respect being a more or less “null” period in which neither energy system predominates. It is in this latter stage that a cell probably is most likely to proceed toward differentiation. Initiation of the differentiation process in a given cell does not necessarily mean, however, that it also loses its ability to regain mitotic competence. This point is particularly obvious in microorganisms where differentiation precedes antephase (see figure 1B). Likewise, in multicellular organisms cells may exhibit a relatively high degree of differentiation and yet still be capable of becoming mitotically competent. While differentiation and mitosis are more or less antagonistic processes, the gain of one potential is possible without loss of the other. It is also not necessary to consider that a differentiated cell must undergo “dedifferentiation” before it can gain mitotic competence. Attainment of this potential could result from the cell proceeding toward mitosis by a pathway which may be regarded as a detour. What appears to be a general situation in the multicellular organism is the further along a cell is in its differentiation the less the likelihood of its regaining mitotic potential. This is more a probability change than an absolute one.

Generally, the nucleus has been treated as if it were nothing more than a sac of genetic determiners and that its role was chiefly that of feeding out genetic information to the cytoplasm. Data from enucleation studies indicate that the relationship between nucleus and cytoplasm plays an important part in determining the overall physiological activity of the cell (Brachet 1957, Mazia 1952). The fact that the nucleus enlarges prior to mitosis suggests that changes, both of a morphological and physiological nature, also occur in the nuclear membrane. This raises the point that the physiological state of the nucleus is probably determined, in part at least, by the degree and kind of changes which occur in the nuclear boundary.
If we assume, on the basis of a considerable amount of evidence, that the major components of the glycolytic cycle are primarily intranuclear then the boundary between nucleus and cytoplasm obviously becomes of considerable importance as a controlling factor in the relation between the two energy-producing systems. One way in which the nuclear membrane could affect this balance would be to alter its permeable properties with regards to oxygen uptake and exit of Krebs cycle intermediates such as pyruvate. In view of the fact that the nuclear membrane has been shown to have a rather bewildering array of permeable properties it is not unrealistic to suppose that permeability changes of the type mentioned above actually do occur. The nuclear membrane would vary from being highly permeable, through differentially permeable, to almost completely impermeable. On this basis, the mitotic competency of a cell, in part, is determined by the relation between nucleus and cytoplasm.

In a tissue mitotic activity is not constant but is periodic. It follows, therefore, that the total mitotic activity is made up of two variables (1) the number of cells committed to mitosis at any one time, and (2) the time between successive commissions. Theoretically, any relationship between these two variables is possible i.e., the number of cells committed may vary independently of the period. Mitotic index *per se* gives no information as to which of the theoretical relationships between the number of cells committed and the period may exist in a tissue at any given time. If one had information concerning such factors as maximum mitotic index (MI$_{mx}$), minimum mitotic index (MI$_{mn}$), and duration of mitosis (T$_m$), then the following relationships could be determined: (1) $N=MI_{mx}-MI_{mn}$, where $N$ is the number of cells committed to mitosis during any one period, and (2) $t_1-t_0=\frac{N\times T_m}{MI_{mx}}$, where $t_1-t_0$ is the time between successive periods of commission and $t_1-t_0\leq T_m$. Although such analysis is applicable to only those tissues which lend themselves to measurement of mitotic activity over a period of time, the relationships involved in such an analysis are, nonetheless, of considerable theoretical importance in consideration of the factors controlling the mitotic cycle. Since the relative numbers of cells in any part of the cycle at a given time will depend on the relationship $t_1-t_0=\frac{N\times T_m}{MI_{mx}}$, it is possible by following changes in this function to detect variations in cell populations within individual segments of the cycle.

Growth of an organism or organ, as well as repair capacity, depends on cell replication which, in turn, depends on cells being able to achieve mitotic competence following cell division. It follows, therefore, that so long as an organ has a repair capacity it must also have a population of mitotically competent cells. Herein lies a neoplastic hazard. It is obvious that if less than one-half of the products of mitosis are committed back to
mitotic competence, repair capacity is diminished. If approximately one-half are recommitted back into mitosis, the status quo is preserved, such as in the case of the root meristem. If more than one-half are committed back to mitotic competence, the division potential is increased. On this line of reasoning, one does not have to assume that a neoplastic potential reflects any inherent abnormality in the cells of the population. That is to say, it is not really necessary to make the assumption that neoplastic growth must take its origin from a cell which has become altered in some way. There are probably certain metabolic conditions in a tissue which may be regarded as being potentially neoplastic, namely, whatever condition favors committing more than one-half of the products of successive divisions back into mitosis. A carcinogenic agent would, on this basis, be any agent which increases the likelihood of cells returning to mitotic competence rather than allowing them to undergo differentiation. This situation could be established in a number of ways. It is, therefore, not surprising that a wide variety of compounds are carcinogenic in nature. Such agents need have little in common with regard to chemical structure.

A high rate of mitosis is not a necessary prerequisite for perpetuation of a neoplasm. In terms of periodicity, commission of small numbers of cells into division at frequent intervals would be compatible with establishment of neoplastic growth. This would be particularly true if such a situation also involved a relatively rapid passage of cells through the so-called resting stage referred to in figure 1A. From consideration of figure 1A, it would appear that the condition most favorable for establishment of neoplastic growth would be a drastic shortening of the time in which the products of mitosis remain in the resting phase. This would not necessarily be a characteristic of the cell per se but rather of the tissue as a whole. The idea that an interval (resting phase) between successive mitoses is necessary for differentiation to occur in the multicellular organism is not a new one. It is well known that division and cell differentiation cannot occur simultaneously and that differentiation always takes place in the period between cell divisions or after division has ceased entirely (Fischer 1946). A secondary but, in theory, important contributing factor in neoplastic development would be the presence of relatively high numbers of mitotically competent repair cells in a cancerous site.

Considerable attention in recent years has been paid to metabolic differences between normal and malignant tissues. While such differences may have considerable value from the standpoint of diagnosis, it is not justifiable to interpret such differences as indicating that the actively dividing cells of a growing neoplasm are physiologically abnormal. As far as cell populations are concerned, both normal and malignant tissues are heterogeneous. For example, a normal tissue might be considered to be composed largely of cells in various stages of differentiation, together with varying numbers of
senescent cells plus some which are in some stage of mitotic competence. A malignant tissue, on the other hand, would appear to consist of a fairly large number of morbid cells, together with a fairly large number of cells in varying stages of mitotic competence. On the basis of almost any kind of metabolic measurement of a tissue, one would expect to find differences between normal and malignant ones (see figure 2). Furthermore, the metabolic activity in any two tissues, malignant or otherwise, need not be the same or very similar (Weinhouse 1955). Much attention has also been paid to abnormal cytological conditions in tumors and attempts made to relate such abnormalities to cancer ontogeny. From our point of view, however, such chromosome or mitotic aberrations are probably nothing more than the end results of abnormal metabolic conditions which undoubtedly must exist in any well-developed neoplastic tissue. In that part of the neoplasm which is actively contributing to its growth, conditions obviously must be appropriate for normal mitosis otherwise perpetuation of the neoplasm would not occur.

As to the problem of cancer therapy itself, there are three levels of attack. The first of these involves the use of surgical excision or irradiation to effect killing of an already formed neoplasm. This approach, although it does not eliminate the neoplastic potential or hazard, has been used extensively to remove neoplastic tissues and to prevent metastases from occurring. Added to this type of therapy in recent years, has been the treatment of tumors with chemical compounds, most of which fall into the class of antimitotic agents. The rationale for their use, like that for irradiation, is to...
effect differential killing of cells of the tumor without doing serious damage to normal body cells. The major hazard involved in the use of such agents is the difficulty encountered in preventing at the same time reduction of mitosis to a point where repair of vital organs is seriously impaired.

The second means of attacking the problem is by way of preventative measures. Of these, the most practical involves the screening of compounds for carcinogenic activity. Many such compounds, once identified, can be avoided by the individual. Those which cannot may possibly be nullified in their effects. A carcinogen which owes its property to its irritating effect may be made less irritating or toxic and hence reduce its carcinogenic potential.

The third and most difficult method of attack is the one most pertinent to the problem of the ontogeny of neoplastic growth. This involves, in brief, the modification of tissue metabolism in such a way that its component cells, especially repair and partially differentiated cells, do not readily regain mitotic competence. Inhibition of mitosis by itself is not the important factor concerned in the prevention of neoplastic growth. What is important is control of the population of mitotically competent cells within a given tissue. Mitotic inhibition is effective only in controlling localized division within an already established tumor. Of more critical significance from the point of view of cancer prevention is the experimental attack on the mitotic cycle as a whole rather than on active mitosis alone for here are found the true parameters of the problem concerning control of normal cell division. Only when these parameters are more precisely defined, both in the morphological and physiological sense, will a more complete understanding of the problem of cancer ontogeny be forthcoming. The most promising approach would, therefore, seem to lie in focussing one’s attention on the metabolic conditions existing during limb and organ regeneration, callus formation in plant tissues, and general repair of other tissues of the organism.

**Literature cited**