INTRODUCTION

This review is concerned with two questions: (a) how can mitosis be modified experimentally and (b) of what value in cancer therapy can such modification be? It pretends to be neither exhaustive nor very systematic.

From one point of view, a great deal of experimental and practical cancer therapy can be said to be antimitotic in effect if not primarily in intent. Any measure that halts growth of cancer cells would necessarily impede their division. Although one might be led to restrict the term "mitotic poisons" to include only those chemical agents that affect cells during the visible prophase-metaphase-anaphase-telophase portion of the mitotic cycle, the newer knowledge that important events of the total mitotic or cell cycle occur during interphase would lead us to do otherwise. Chèvremont (16) has pointed out that a toxic substance that suppresses growth or inhibits metabolism is not to be considered an antimitotic agent, properly speaking. I find this distinction sometimes difficult to draw; but our interest in the cancer field is to a considerable extent in end-results.

The literature of experimental cancer chemotherapy lies open to the inquiring student of mitosis. Mazia (48) has written that review of the vast literature on mitotic stimulation and inhibition by such agents as carcinogens, antimitotic drugs, hormones, and radiation might provide important clues to the biochemistry of cell division. This literature is vast, indeed, as anyone who glances through the products of the abstracting services can see.

One is sometimes tempted to think of cancer cells, apart from any question of the normality or abnormality of their other attributes, as growing and dividing beyond any possible need of the body, and of cancer as a disease of excessive mitosis. Recent work of Malmgren and Mills (45) tends to support this view: a liver mitotic stimulant, rich in nucleic acids, which they found in tumors, was detectable in normal tissues only after treatment that might have destroyed an inhibitor or released the stimulant from a suppressing complex. The concept of cancer cells expressed in Swann's review (71) was also of this nature: Swann looked on cancer cells as becoming "streamlined" for proliferation by natural selection in a varying population.

If cancer is regarded as a disease of excessive mitosis, then restraint of mitosis would be the direct therapeutic measure. This restraint of mitosis, however, must be selective. Otherwise, for the organism as a whole, the therapeutic gain from inhibition of mitosis in cancer cells may be offset by a loss from the restraint of cell division in those tissues in which the continued production of new cells is a necessity for bodily well being, such as certain epithelia and the blood-forming regions.

It may be questioned whether absolute selectivity against cancer cell mitosis has ever been achieved. There are reports, of course, concerned with individual tumors, such as that from France (14), which reported selective inhibitory effects of estradiol and testosterone on HeLa cells in culture, including reduction of mitotic index, with no restraint on normal uterine epithelium in culture. Welch (76) has pointed out in a recent review...
that there is at least one chemotherapeutic agent capable of selective action on certain neoplastic cells and without harmful effect on proliferating normal cells of man: namely, 6-azauridine. It must be remarked, however, that pregnancy in mice can be interrupted by this agent (63). Although Taylor et al. (72) found that 6-azauridine was without effect on mitosis in bean seedling roots, perhaps because the cotyledons had an adequate reserve of pyrimidines, I would expect that, under other circumstances, 6-azauridine might be found to inhibit certain interphasic syntheses that are necessary preliminaries to mitosis. Its active derivative, the 5'-phosphate, interferes in the de novo pathway of nucleic acid pyrimidine biosynthesis (76). Its free base, 6-azauracil, upsets proper chromosome movement in the mitotic apparatus in onion root cells (44).

For cancer therapy, however, it may be only relative selectivity that is needed, and this may be obtained to some degree by such means as localized irradiation (to mention another sort of therapy) or the infusion of tumorous regions of the body with chemical agents.

What about the possibilities of experimental modification of mitosis? Nature has already shown us, with modifications that occur in the normal course of events, that the possibilities are numerous. To cite an extreme example, one could mention meiosis in the formation of germ cells. The reduction division of meiosis, with its prolonged prophase, synopsis of homologous chromosomes, and their separation to opposite poles, may be regarded as a derivative or variant of mitosis; and in oogenesis the unequal cell division by which small polar bodies are cut off from their much larger sister oocyte merely emphasizes the difference from the usual mitotic division in somatic cells. Endomitosis, or other endoreduplicative phenomena, by which regular polyploid series of nuclei are built up in some organs, including mammalian liver and the nurse cells of the dipteran ovary (57), furnishes an example of the normal suppression of the achromatic apparatus. The building up of polytene chromosomes in some insect tissues is a related phenomenon (58). What could be more bizarre than the mitoses in which certain chromosomes are eliminated from the somatic cell lines of certain organisms (56)? The answer is, perhaps only the spermatogenic divisions in the fungus fly, Sciara, in which the chromosomes of paternal origin appear to back away from the single center of the division figure, only to be discarded (49). Here we see that a chromosome is not merely a chromosome—it is also its environment in a previous generation, may have a determining influence on its behavior now. Somewhat similarly, with respect to environment here and now, one X-chromosome may undergo heteropyknosis to form the sex chromatin body, if the resting nucleus contains another X-chromosome, as Ohno and Hauschka (54) have determined.

This is not to say that the mitosis-wreckers in laboratory smocks have as yet achieved such startling results. It does tell us that much is possible in the modification of mitosis and chromosomal behavior, if we but knew how.

What sorts of mitotic effects do we usually recognize in our treated cells, in our tissue cultures, in our sectioned tissues (9)? There may be, first of all, a change in frequency of mitotic figures. There may be a wave-like increase of mitoses resulting from stimulation (or release from inhibition), or there may be an only apparent increase in mitotic rate resulting from the accumulation of mitotic figures blocked in some recognizable stage. The best-known block is the metaphase arrest. There may be accumulations in other stages, as in prophase, or of the pseudoprophases that pile up from treatment with ribonuclease (17). There may be a decreased frequency of mitotic figures because of arrest at some point in interphase, perhaps from inhibition of some essential synthesis by some preprophasic (i.e., interphasic) inhibitor. Damage to chromosomes may be observed in metaphase or anaphase; chromosome breaks, chromatid breaks, various sorts of rearrangements, fragmentations, chromosome bridges, and chromosomal "stickiness" may be evident. Chromosomes may be lost, or fail to divide, or move precociously to the poles, or fail to move to the poles. Mitoses may be multipolar, and daughter cells formed in irregular number may have irregular numbers of chromosomes. Cells may become pyknotic and die at various stages of the cell cycle. In short, it appears that we can merely make accidents happen, increasing in fact the frequency, often not inconsiderable, with which these same mitotic abnormalities spontaneously occur in the cells of many cancers (10).

**AGENTS THAT MODIFY MITOSIS**

Most investigators, when confronted with the welter of data on effects of agents on mitosis, find themselves impelled to classify. First let us consider the agents themselves.

A primary step in classification would be to set stimulators apart from inhibitors, disregarding the pharmacological dictum about stimulation from minute quantities of inhibitors. I have little to say about agents that stimulate mitosis, because with
reference to cancer therapy they have the opposite of what appears to be the desired effect. This is the case, unless one wishes to follow the novel proposal of Berglas (7) and induce cancer cells to divide themselves to oblivion. That there may be merit in this general idea is seen from the work of Braun (15): hypothetical epigenetic particles responsible for the tumorous nature of crown-gall cells did not divide as rapidly as the cells containing them, and thus “cured” cells could be obtained. What of the possibility, moreover, that cancer chromosomes have some, not high, degree of multiple-strandedness, and that the chromosomes might be induced to divide down through this strandedness more rapidly than the strands could be replicated? This possibility is suggested by Lindner’s work (42) with 5-fluorouracil treatment of Ehrlich ascites cells, which suffered a decrease by one-half in DNA per cell with no drop in number of chromosomes. I am reminded of my own dissertation research (19), which suggested a moderate polyteny in cancer chromosomes. The 5-fluorouracil is an inhibitor, of course, but relative to it the normal set of circumstances in proliferating Ehrlich cells constituted stimulation; shifting the base-line allows us to think in terms of relative stimulation in this case.

Stimulators of mitosis have been considered by Swann (71). He wrote of hormones, of special substances for each cell type, and of the stimulus to cell division as partaking of the nature of an inductive phenomenon, with the cell being steered away from synthesis supporting its previous differentiated function and toward synthesis of the materials needed for cell division, such as replicated chromosomes and a mitotic apparatus.

A few specific agents capable of stimulating mitosis may be noted. Agmatine, or decarboxylated arginine, was shown by St. Amand, Anderson, and Gaulden (69) to speed up mitotic activity in grasshopper neuroblasts; it had been chosen for test in the light of a theory of mitosis initiation based on polycation-polyanion balance (3). Phytohemagglutinin, a mucoprotein from beans, induces mitotic activity in peripheral leukocytes in vitro, or at least puts them into a state conducive to mitotic activity (52), and the glucocorticoid, prednisolone 21-phosphate, tends to prevent this change (53). Administration of thymidine to adult mice speeds up mitotic activity in their intestinal crypts, where the methylation reaction for the production of thymidine for DNA is thought to be rate-limiting (52). For plant cells, there is the well known influence of kinetin, or 6-furfurylaminopurine (50). Finally, this audience is hardly the one to forget the mitotic stimulation that occurs in mouse epidermis shortly after it is painted with carcinogenic hydrocarbons (61).

A second step in classification would be to consider the nature of the agents, and initially whether they are physical or chemical. Among the physical agents are various forms of radiant energy, sonic vibrations, and the like. The mechanisms of action include gross denaturation, as by microbeams of ultraviolet (25); scission of the DNA double helix (46); thymine-dimerization in DNA, by ultraviolet (8, 75), which could involve cross-linking of strands; hydration of the cytosine ring in DNA under the influence of ultraviolet (77); formation of free radicals (39, 59), of peroxy radicals (18), of peroxides (66, 79), and of derivatives of nitrogenous base precursors of nucleic acids (70).

An analysis of the mechanisms of cell death from radiations, and of the part played in this by mitosis or attempts at mitosis, has been presented by Howard (34). She reviewed the evidence that the site most sensitive to radiation in the cell is the nucleus. Mitotic delay is produced more effectively by ultraviolet irradiation of the nucleolus than of other portions of the nucleus in the grasshopper neuroblast, according to Gaulden and Perry (30); when the microbeam was applied during the period from late telophase to mid-prophase, mitosis could be permanently halted. Howard (34) suggested, therefore, that nuclear RNA and possibly also DNA might be involved in mitotic delay from irradiation. Mitotic inhibition was not accounted for by delay in synthesis of new DNA (and this is also the conclusion of Albert and Das [2, 19]). When DNA synthesis was delayed by irradiation, however, this might result from an untoward effect on nuclear phosphorylation. Loss of viability of a cell line was probably produced by chromosomal structural changes. Errors in replication ultimately caused by traversal of the template by an ionizing particle could lead to chromosome breakage. Studies of the loss of reproductive ability with respect to ploidy suggest that it is the result of upsets in genomic balance. Daughter cells resulting from mitosis of irradiated cells would receive effectively unbalanced genetic complements and might shortly die out. Death might not literally ensue, however, until several cell generations have passed (24). Reversible mitotic delay in S3 HeLa cells given low doses of x-ray has been attributed to chromosomal damage expressed in interference in the condensation of chromosomes in the G2 period (80).

The state of nutrition can influence the response of cells to irradiation. Alexander and Mikulski (1) found that, with lymphoma cells growing in a completely adequate medium, all
cells divided at least one time, after receiving x-ray doses up to 500 r, before autolyzing; but with lymphoma cells growing about half as rapidly in a restricted medium, death usually occurred in the absence of any mitosis or attempt at division. They concluded, therefore, that for the latter cells chromosomal injury was not involved in death to an important extent. Howard (34) has also remarked on the great radiation-sensitivity of small lymphocytes, despite their mitotic inactivity.

It is intriguing that some of the effects of physical agents are mediated by altered chemicals from the cellular environment or from the cells' own stock of metabolic intermediates. In short, we are provided with a ready-made transition to a consideration of chemical agents that influence mitosis.

The chemical agents that affect mitosis include various alkylating agents; some quinones; certain alkaloids; carbamates; respiratory poisons; certain antibiotics; a variety of analogs of amino acids, vitamins, and precursors of nucleic acids; and others (9).

These heterogeneous chemicals can be further classified from the physiological or mitotic-pharmacological point of view. Our current interpretations of the actions of mitotic inhibitors are influenced by newer knowledge of the cell cycle—i.e., of the total mitotic cycle including the triply-partitioned interphase between telophase and the following prophase. Mitotic poisons can be classified by the stages they affect—by the stages in which their actions cause the mitosis to be delayed or arrested. Mitotic poisons can also be roughly classified by the site of their major effects in the cell, as on the chromosomes or on some part of the achromatic apparatus, for example.

Thus Sentein (65), using the segmenting egg of the urodele as his biological test system, has classified antimitotic agents into three categories: spindle poisons, chromosome poisons, and agents of mixed effect.

Among the agents whose primary effect was depolarization of the spindle, Sentein (65) included (a) the slowly reversible agents, colchicine, its derivatives, podophyllin, and podophyllotoxin (the latter two could also cause secondary breakage of chromosomes); (b) agents of moderate reversibility, such as chloral hydrate, which produced monocentric mitoses and some chromosome breakage; (c) rapidly reversible ethyl-, phenyl-, and monomethylurethanes, which also damaged chromosomes; (d) feebly acting sodium cacodylate, sarcomycin, aloin, and phenylamino-propane sulfate—these affected cleavage; and (e) patulin, a lactone, which was also a strong chromosome poison.

The agents whose primary effect was on chromosomal integrity included triethylene melamine, nitrogen mustard, and various ethyleneimino-quinones, which might also influence the achromatic apparatus.

The substances of mixed and complex effects on spindle, nucleus, and chromatin included phenol and various of its derivatives, some khellin derivatives, para-aminosalicylates, phenylmercuric borate, and caffeine.

It is noteworthy in this classification by Sentein that nearly all agents had multiple effects, not merely those in the third category. This fact should help to dispense with over-simplified notions about the mitotic poisoning actions of chemicals.

It is not only with respect to site of action that there is heterogeneity of effect; this is also true for stage of action. Sentein (65) objected to calling colchicine purely a metaphase poison, because his material included arrested pro-phases, anaphases, and telophases as well as C-metaphases. Lehmann (41) raised a similar objection to terming colchicine purely a spindle poison, because in Tubifex eggs it appeared to affect the centriole in stages prior to development of the spindle.

The centriole, we must note, has been suggested by Mazia (47) as perhaps a most logical target of antimitotic action, as its duplication appears to lead the way in mitosis. Rustad (62) has marshaled evidence in support of the concept of division delay resulting from an effect of x-rays or ultraviolet on replication or separation of the centrioles. Because acridine orange produces a similar effect, it was suggested that the damage to the centriole might be mediated by interference in nucleic acid metabolism. This is an attractive hypothesis, but it should be recalled that Fogg and Warren (26) in 1941 found an x-ray dose of 2,400 r to Sarcoma 180 or Walker 256 tumors to increase frequency of cells with more than two centrioles considerably, as though centriolar duplication had not been inhibited by the treatment.

Other examples may be given of multiple stages and sites of sensitivity to antimitotic agents. Actidione appears to act at several stages in the mitotic cycle (33), and its effects include a prophase arrest. Maleuric acid was reported (55) to inhibit not only DNA synthesis in Ehrlich ascites tumor cells, but also progression through the G2 period of interphase into prophase, as well as passage through metaphase. Among the effects of antifolic acids that have been described in various mitotic systems (9) are interphasic inhibition, ex-
pressed as a general decrease of mitotic incidence; a metaphasic arrest in certain cells (6, 36); delayed, three-group metaphases in cultured H.Ep. \#2 cells (11), and chromosomal damage in certain tissues (23, 73). A dissent should be noted: Gelfant (31) has failed to confirm the effects of maleic acid and the metaphase arrest by antifolies in excised mouse ear epidermis.

A comprehensive study by Deysson and Truhaut (20) of the mitotic effects on plant root tips of a variety of agents used in experimental cancer chemotherapy is noteworthy. The agents tested included mustards, ethyleneimine compounds, urethans, certain antibiotics, and various purine and pyrimidine bases. Compounds of these several classes tended to have similar effects. At the lowest active concentrations (about $10^{-4}$ M for the urethans and about $10^{-7}$ to $10^{-9}$ M for the others) there was a depression of mitotic incidence. With progression to higher concentrations, chromosomal breakage and bridge formation set in. At higher concentrations, all entry into mitosis was prevented as the result of preprophasic inhibition. Still higher concentrations or prolonged exposure caused cell death. Near the lethal concentrations, a few compounds among those tested produced spindle inhibition or prevented cytokinesis. It was of interest that the so-called "radiomimetic" agents and the presumed antimetabolites had no essential differences in effect. All of them were preprophasic poisons, and most of them damaged chromosomes. Very few of them damaged both chromosomes and spindle, and in this respect the findings of Deysson and Truhaut are not in strict accord with those of Sentein (65). Poussel et al. (58) have also found alkylating agents and antipurine agents to have much the same final effects.

This should not be taken to mean that nucleic acid base analogs and alkylating agents necessarily have the same mechanisms of action. Perhaps it means that the cell has limited morphological avenues down which to move in response to different agents. Nevertheless, it is well to bear in mind the findings of Lorkiewicz and Szybalski (43) that triethylene melamine reacts primarily with phosphorylated pyrimidine precursors of DNA, converting thymidylate into a potent mutagen, rather than with DNA itself.

We are still much in the dark with respect to the mechanisms of action of many antimitotic chemical agents. For some that are known to be mutagenic or to interfere in nucleic acid metabolism, we suspect that an attack on DNA or in some cases on RNA is the basis for the antimitotic effect. For others an interference in the synthesis of special proteins is suspected. There may be interference at a higher level, too, in putting together the structural components of the chromosomes or of the achromatic apparatus. Perhaps colchicine and other C-mitotic agents operate at this level of interference in intermolecular bonding (64), but exactly how is not known.

Discussions of the mechanisms of action of nitorgen mustard and other alkylating agents in their inhibition of cell division have tended, despite the high reactivity of these agents with many molecular constituents of cells, to center on their reactions with nucleic acids. There are conflicting claims, such as that DNA synthesis may be inhibited or stimulated by alkylating agents. Gelfant (31) has attempted to resolve these discordant reports by suggesting that nitrogen mustard, for example, inhibits cell division during the G1 period of interphase and not in the preceding S period of DNA replication; it is only because passage into the first mitosis and subsequent cycles is prevented that there is an illusion of the inhibition of DNA synthesis. In some respects, then, there is a parallel to the effects of x-rays. It is difficult to anticipate, however, that DNA cross-linked by bifunctional alkylating agents (68) could be replicated to completion. In this connection we should consider Auerbach's statement (5) that the induction of mutation by alkylating agents need not occur by cross-linking, because certain monofunctional agents are highly mutagenic.

Another interesting parallel between the effects of x-rays and radiomimetic chemicals is seen with respect to the state of nutrition of treated microorganisms: after treatment, starved animals exhibit immediate delay of cell division, whereas well nourished animals go through a division or two before inhibition (60).

Another parallelism may exist in the repair of DNA damaged by irradiation or by chemical agents. Chèvremont (16) has reported an interesting phenomenon in certain cells that remain mitotically active in cultures of chick fibroblasts despite inhibitory treatments with the alkylating agent Myleran. In the presence of Myleran, these cells quadruple their DNA content instead of merely doubling it in preparation for mitosis. Chèvremont suggested that the Myleran damages the old DNA, which the cell replaces, not by replication with the existing material as a template, but by another process, in which the mitochondria may participate. This hypothesis reminds one of that advanced by Doudney (32), according to which there are two mechanisms for synthesis of DNA, a primitive "mutagenic" mechanism involving coding transfer of new DNA through an intermediate RNA-protein structure, and the
“Kornberg mechanism,” which can be blocked by cross-linking of DNA strands by ultraviolet and can then be photoreactivated with white light.

Taylor et al. (72) have an illuminating interpretation for this problem, based on their work with 5-fluoro-2'-deoxyuridine (FUDR) and x-radiation. It is that DNA polymerase repairs and rejoins DNA with broken chains. Single strands grow in one direction, copying the antiparallel strand, to repair the break, and the broken pieces are discarded, perhaps as single-stranded fragments. It will be recalled that Anderson (8) proposed that the discarding of defective DNA strands might occur during chromosomal condensation; the presence of these defective strands would explain chromosomal “stickiness” after damage. It is in the sense of a repair of broken and frayed strands, which make more primer DNA available, that the recent finding of Alfert and Das (2, 19) that x-radiation accelerates DNA synthesis in the early part of the S period can be interpreted.

An interesting aspect of Taylor’s hypothesis (72) is that chromosomal repair, although involving DNA polymerization, need not be restricted to the S period of DNA synthesis during the cell cycle. Sheldon Wolff (78) has remarked on chromosome repair as involving protein synthesis rather than DNA synthesis, because it goes on at all stages of the cell cycle and is prevented by inhibitors of protein synthesis. It is sensitive to various metabolic inhibitors and is stimulated by exogenous adenine triphosphate. Perhaps some of the protein involved is part of the machinery for repair, however.

It is difficult to assess our current understanding of the actions of certain groups of antimetabolites with respect to cell division. Purine analogs, for instance, may interfere in the biosynthesis and utilization of normal purines and thus depress the synthesis of nucleic acids; if they are incorporated into nucleotides and polyribonucleotides, fraudulent coenzymes and nucleic acids may result (9, 74). It has been suggested (4) that 6-mercaptopurine riboside triphosphate, formed in vivo from 6-mercaptopurine, may inhibit the formation of the nicotinamide nucleotide coenzymes I and II. This possibility is not easily reconciled with the theory of Morton (51) that mitosis is initiated when diphosphopyridine nucleotide (DPN) concentration falls to a critically low level, or with the theory of Fujii (29) that nicotinamide inhibits mitosis by inhibiting DPNase activity and thus allowing the intracellular concentration of DPN to increase.

Consideration of 2-aminopurine may put us on more solid ground. This agent is very active in mouse tissue cultures (12), producing chromosomal bridges and breaks and many lagging chromosomes that lie near the spindle poles instead of on the equatorial plate. This abnormality is related to the “two-group metaphase,” which is often delayed in passage to anaphase (11).

It would be interesting to ascertain whether the considerable activity displayed by 2-aminopurine in the production of mitotic abnormalities is related to the observations by Freese (27, 28) on mutagenesis by this agent. 2-Aminopurine, incorporated in place of adenine in DNA, can hydrogen-bond with and lead to the incorporation of hydroxymethylcytosine in the new complementary strand of DNA in bacteriophage T4. Thus, an adenine-thymine base pair can be changed, over several cycles of DNA replication, to a guanine-hydroxymethylcytosine pair in this phage and presumably to a guanine-cytosine pair in organisms with more conventional nucleic acid bases. This change constitutes a genetic mutation.

The cytological effects of base pair-shifting mutagens are under study by Hsu and Somers (35). An outstanding effect of the thymidine analog, 5-bromo-2'-deoxyuridine (BUDR), was the stretching of kinetochore regions and secondary constrictions. Chromosome breakage and translocation occurred at these sites, as well as at telomeres and a few other regions; which Hsu and Somers suggested might contain high concentrations of adenine-thymine pairs, with much of the thymine replaced by 5-bromouracil by this treatment. The instability basic to the grossly visible chromosome damage appeared to result immediately from the incorporation of BUDR into DNA, because chromosome breakage was manifest in cells of a hamster cell line in the first metaphase succeeding exposure to BUDR during the S period 6 or 8 hours before (67).

Fluorodeoxyuridine, whose mechanism of action involves production of an endogenous thymidylate deficiency, has been applied to Vicia faba seedling roots by Taylor et al. (72). Chromosome breaks and gaps (interpreted as relatively uncoiled single strands of DNA) were noted in the mitotic figures after 3 or 4 hours. The extreme effect of shattered chromosomes in anaphase had much the appearance of the superfragmented mitoses Koller (40) noted in Walker carcinoma 256 cells after treatment with certain alkylating agents, and which he attributed to metabolic disturbances beyond the truly radiomimetic effect. Chromosomal fragmentation and anaphasic bridging caused by treatment with FUDR and its 5'-monophosphate
were noted by Biesele (11) in H.Ep. #2 cultures, as well as some three-group metaphases and delayed metaphases with scattered chromosomes.

In H.Ep. #2 cultures, BUDR was less inhibitory than FUDR (11). BUDR relieved some of the metaphase arrest produced by aminopterin, and cultures treated with both agents together contained anaphases and telophases with chromosomal bridges and fragments. By itself, BUDR had little effect; but this exposure was for 24 hours only, and Hsu and Somers (35) found that strain L cells show low frequency of chromosomal breakage during the first 10 days of exposure to BUDR. Djordjevic and Szybalski (21) also noted few chromosome breaks in the treated human cell line D98S, but they did observe a great increase in sensitivity to ultraviolet radiation.

DISCUSSION

What is to be made of all this? We have considered only a small percentage of even the relatively recent data, concepts, and hypotheses that bear on our subject. Even so, what conclusions can be drawn about the therapeutic application of experimental modifications of mitosis in cancer cells?

Before drawing conclusions, I would state my conviction that cancer cannot be looked on simply as a disease of excessive mitosis. This oversimplified view can hardly gain adherents. In treating cancers with antimitotic agents per se one is probably treating a major symptom rather than the disease. It would be our hope that alleviation of this symptom would indicate that one is on the right track toward a definitive therapy. On the other hand, the distinct possibility must be acknowledged that the mechanisms of therapy of some agents may differ from the mechanisms by which they exert their effects on mitosis. For example, Johnson and co-workers (37) considered the C-mitotic effect of vincaleukoblastine to be only coincidental with the tumor-inhibiting properties of this agent. Koller (40) concluded that the inhibition of growth in experimental tumors by means of alkylating agents was not brought about solely by the radiomimetic injuries to the chromosomes. In comparing a number of related alkylating agents, Koller saw that growth was probably also suppressed by mitotic inhibition, interphasic pyknosis, and stromal reaction. Two isomers producing equal chromosomal damage were not necessarily equal in suppressing tumor growth.

Be that as it may, it appears that chromosomal damage probably plays some role in cancer therapy, whether for mechanical reasons, such as those having to do with cross-linking or with dicentric chromosomes and bridge formation in anaphase, or for genetic reasons, with nonviable gene combinations resulting from abnormal mitosis or from gene mutations.

In the matter of gene mutations, there are several aspects to be considered. Some mutations may be produced directly, whereas others may require mitosis to become established. With mutagens that shift base pairs, for example, several cycles of DNA synthesis after the base analog has been incorporated may be required to establish the altered base pair, and a cell division may be needed to have the mutation come to expression.

As for chromosomal breakage after incorporation of an analog, subsequent DNA syntheses with certain illicit replications may not be needed, according to the work of Hsu and Somers. Chromosomal breakage in sites of considerable analog incorporation may occur in the course of mitosis, however, by virtue of the locally changed physical properties of the chromosomes and their response to the tensions and stresses of chromosomal condensation incident to mitosis.

Once chromosomal or genic imbalance is experimentally established in tumor cells, does that contribute to therapy? Certainly, nonviable chromosomal or genic combinations may be set up, just as they often arise spontaneously in tumor cells; but it is also possible that the genetic instability will contribute to tumor progression, greater malignancy, and the origin of new stemlines resistant to one means of therapy or another.

In the research we have considered above involving radiation, it is evident that cell death or reproductive incapacitation induced by irradiation can occur either in the absence of mitosis or after mitotic activity, the abnormality of which we may consider as contributing to extinction of the cell line.

In summary, mitosis may be a point of weakness and a good point of attack against cancer cells, just because proliferation is one of their common and prime concerns; mitosis may be a necessary means to cell death through incorrect or inadequate replication of DNA; mitotic disturbances may help to establish unbalanced and nonviable chromosome complements in daughter cells by one means or another; but at the same time it is evident that cell death can be produced by some of the agents concerned without recourse to mitosis. The mechanisms of action involved in successful cancer therapy with these agents may not be the same as those by which they derange...
mitosis, or therapy and mitotic derangement may be coincidental. In any event, our level of understanding needs to be raised with respect to fundamentals of cell division, mitotic poisoning action of drugs, radiation effects, and cancer therapy—all four.

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Experimental and Therapeutic Modification of Mitosis

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