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Mitotic Disrupter Herbicides¹KEVIN C. VAUGHN and LARRY P. LEHNEN, JR.²

Abstract. Approximately one-quarter of all herbicides that have been marketed affect mitosis as a primary mechanism of action. All of these herbicides appear to interact directly or indirectly with the microtubule. Dinitroaniline and phosphoric amide herbicides inhibit microtubule polymerization from free tubulin subunits. Because of the loss of spindle and kinetochore microtubules, chromosomes cannot move to the poles during mitosis, resulting in cells exhibiting an arrested prometaphase configuration. Nuclear membranes re-form around the chromosomal masses to form lobed nuclei. Cortical microtubules, which influence cell shape, are also absent, and, as a result, the cell expands isodiametrically. In root tips and other structures that are normally elongated, these herbicides induce a characteristic club-shaped swelling. Pronamide and MON 7200 induce similar effects, except that tufts of microtubules remain at the kinetochore region of the chromosomes. The carbamate herbicides barban, prophan, and chlorprophan alter the organization of the spindle microtubules so that multiple spindles are formed. Chromosomes move to many poles and multiple nuclei result. Abnormal branched cell walls partly separate the nuclei. Terbutol induces "star anaphase" chromosome configurations in which the chromosomes are drawn into an area at the poles in a star-like aggregation. DCPA's most dramatic effect is on phragmoplast microtubule arrays. Multiple, branched, and curved phragmoplasts are found after herbicide treatment. These disrupters should prove to be useful tools in investigations of the proteins and structures required for a successful cell division. Nomenclature: Barban, 4-chloro-2-butynyl 3-chlorophenylcarbamate; chlorprophan, 1-methylethyl 3-chlorophenylcarbamate; DCPA, dimethyl 2,3,5,6-tetrachloro-1,4-benzenedicarboxylate; MON 7200, 5,5-dimethyl-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarbothioate; pronamide, 3,5-dichloro (*N*-1,1-dimethyl-2-propynyl)benzamide.

Additional index words. Chromosomes, microtubules, microtubule organizing centers.

INTRODUCTION

Many herbicides affect the ability of a cell to enter mitosis by limiting something required for the mitotic process. For example, the inhibition of amino acid biosynthesis by sulfonyleurea herbicides leads to a quick lowering of the number of cells entering mitosis (22). However, there are a number of herbicides that specifically disrupt mitosis or cytokinesis as a mechanism of action. The study of the effects of these herbicides has not only shown us much about herbicide action but also which proteins and structures are required for mitosis in plant cells.

Microtubules. Most of the herbicides that affect mitosis do so by affecting the cellular structure known as microtubules. Consequently, a brief review of microtubules is in order. Microtubules are hollow cylinders with an external diameter of 25 nanometers (Figure 1). They range in length up to 200 microns, although microtubules of this length are rarely detected. The microtubules are primarily composed of the dimeric protein tubulin, which is composed of similar but distinct subunits of 55 kilodaltons each (33). The microtubules of most species are made up of 13 protofilaments, which can be seen in cross-section in favorably fixed material (Figure 1B). Other proteins, termed microtubule associated proteins (MAPs)³ may also interact with the microtubule, sometimes crosslinking the microtubules to each other. MAPs have only recently been identified in plants (4).

Electron micrographs of microtubules, such as those in Figure 1, are "freeze frames" of a very dynamic structure. Microtubules grow by the addition of free tubulin heterodimers (or perhaps small aggregates) to the growing (+ or A) end of the microtubules. Growth requires guanosine triphosphate. At the - or B end of the microtubule, the tubulin subunits are lost. This process is called treadmilling and has been verified *in vitro* but not *in vivo*. A new theory of microtubule growth called dynamic instability (16) retains the ideas of + and - ends of the microtubule but also allows for a dramatic loss of the entire microtubule or parts of it. Dynamic instability has been demonstrated both *in vivo* and *in vitro*. Cellular factors, such as calcium concentration, GTP, and MAPs, all influence the extent of the polymerization and depolymerization.

Microtubules exert much of their influence on cellular processes by acting in groups rather than singularly. In higher plants, there are four arrays of microtubules: cortical (interphase), preprophase, spindle, and phragmoplast (Figure 2) that enable microtubules to perform a variety of cellular functions (Table 1). How these microtubules are organized into arrays is not clear, however. Unlike the case in animal cells in which centrioles at the poles of the cell organize spindle microtubule arrays, there is no corresponding microtubule organizing center (MTOC)³ at the poles in plant

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³Abbreviations: MAP, microtubule associated protein; MTOC, microtubule organizing center; ER, endoplasmic reticulum.

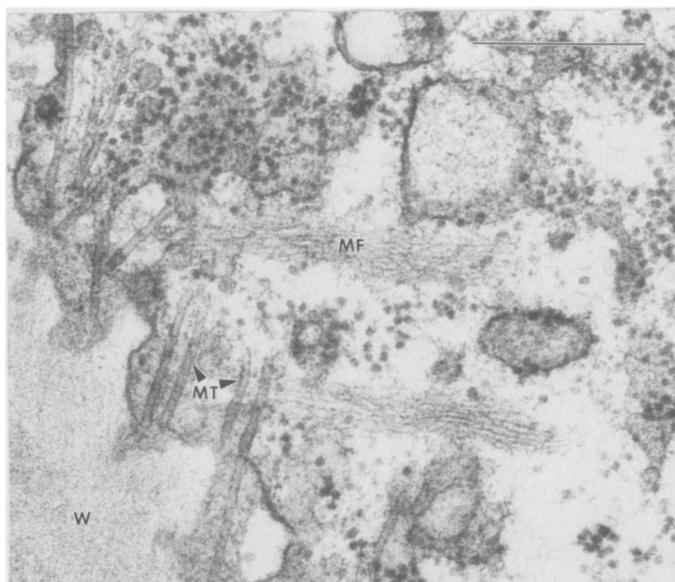


Figure 1. Electron micrograph of an oat (*Avena sativa* L.) coleoptile showing profiles of microtubules (MT) and bundles of microfilaments (MF). Bar = 0.5 μ m.

cells. Endoplasmic reticulum and the nuclear envelope are often sites where microtubules originate (6, 31). When all the microtubules in a cell are destroyed by various agents but then allowed to recover, kinetochores, nuclear envelope, and the plasma membrane are areas where microtubules return (3, 5). Thus, Falconer et al. (5) refer to them as "nucleating sites" rather than MTOCs. This is an area of the plant cytoskeleton that obviously needs more research.

Microtubules are not the only component of the plant cytoskeleton. Microfilaments (Figure 1), composed of actin, are involved in cytoplasmic streaming and possibly the positioning of organelles in the cell. These microfilaments are much thinner than microtubules, although frequently they appear in bundles. Microtubules and microfilaments are frequently found together in the cell and they may work together in some processes, such as chromosome movement during mitosis.

Dinitroaniline herbicides. *Morphological and cytological effects.* Dinitroaniline herbicides are the largest group of herbicides that disrupt mitosis and it is also the group about which the most is known. Dinitroanilines include the heavily used herbicides trifluralin, oryzalin, and pendimethalin. These

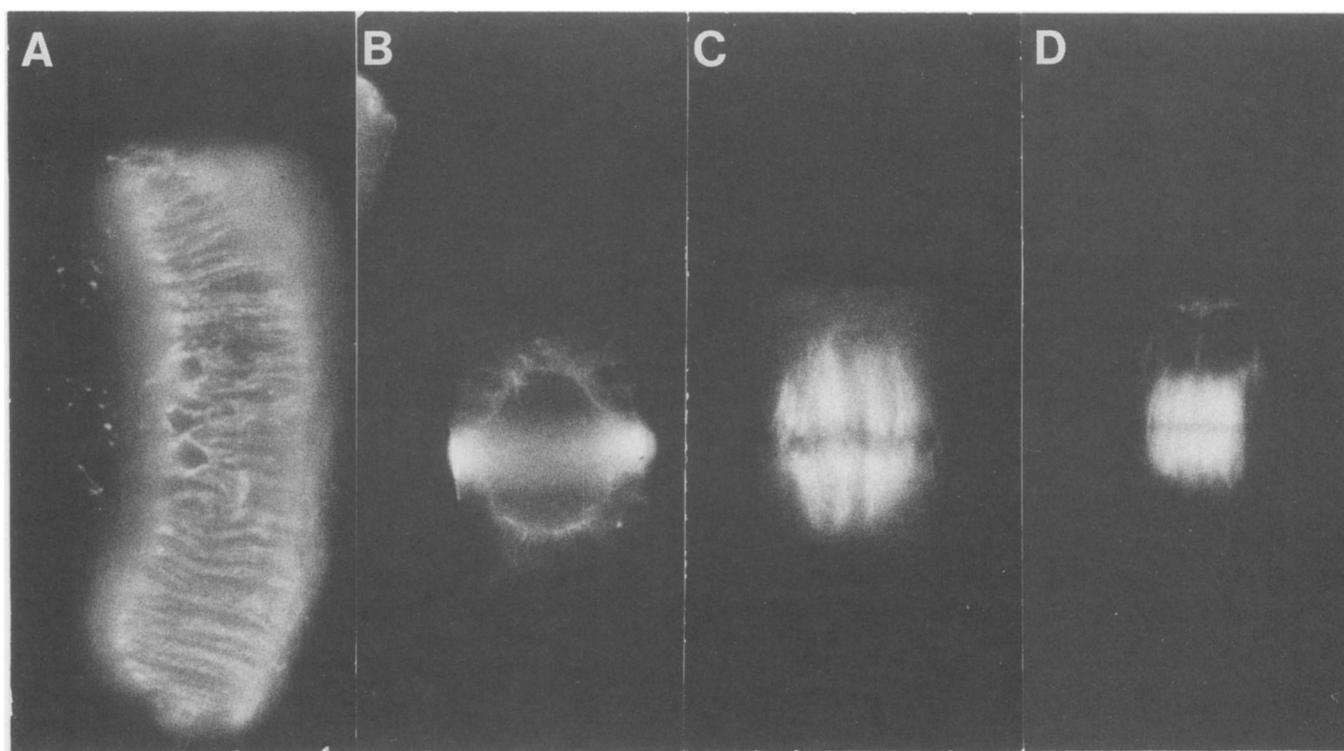


Figure 2. Immunofluorescence micrographs of onion (*Allium sativum* L.) root tips probed with anti α -tubulin revealing the microtubule arrays found in higher plants. A. Cortical microtubules. B. Preprophase band. C. Spindle and kinetochore microtubules. D. Phragmoplast microtubules. $\times 800$.

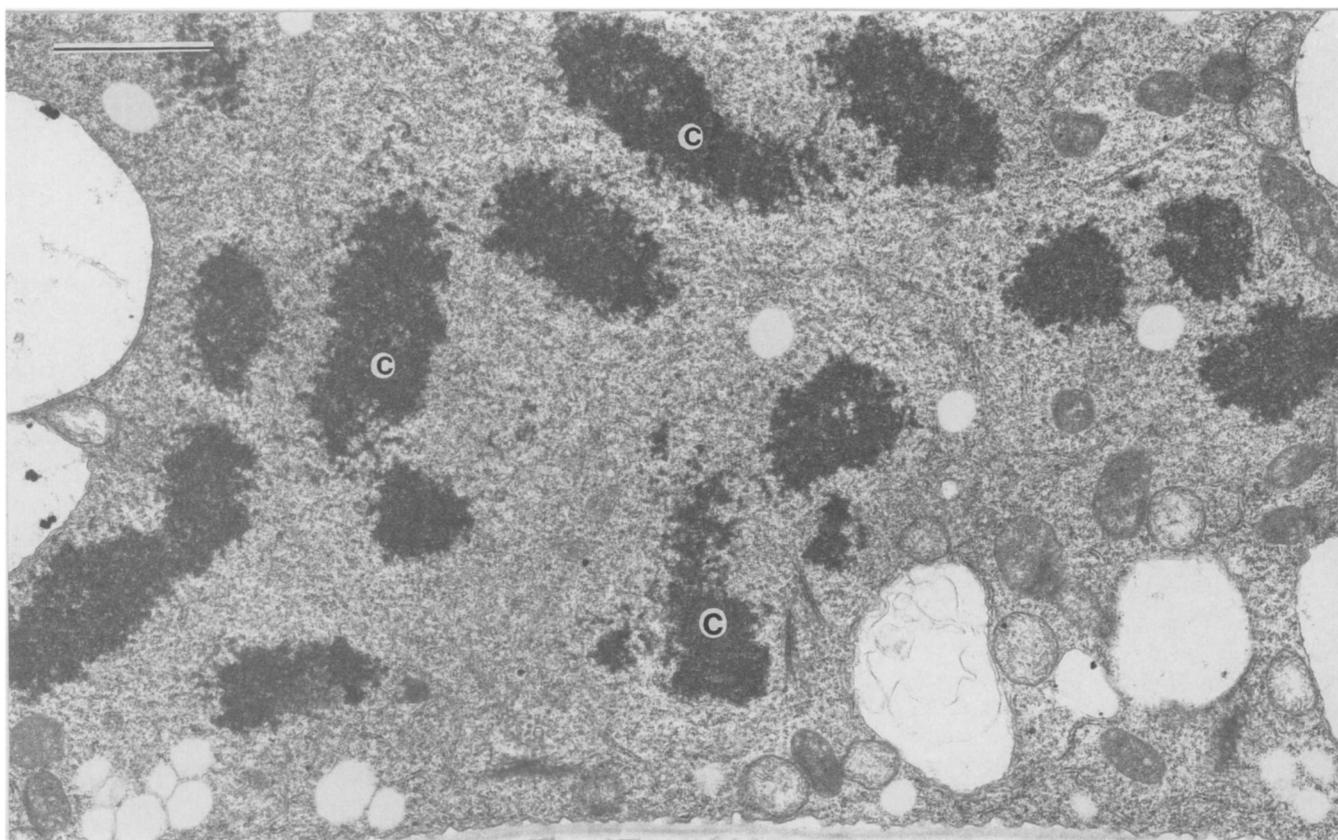


Figure 3. Electron micrograph of onion root tip after a 24-h treatment with 10 μM oryzalin. Characteristic “C-metaphase” or “condensed prometaphase” configuration of chromosomes after treatment with dinitroaniline herbicides. C = chromosome; bar = 2.0 μm.

herbicides are utilized primarily as preemergence herbicides for grass control in dicot crops, such as cotton or soybean.

Roots of susceptible plants are club shaped after treatment with dinitroaniline herbicides (8, 30). The root tip is swollen and the zone where the root hairs are formed is closer to the tip than in untreated controls. The bases of grass shoots are also swollen, giving a bulbous appearance to this area. Both root and shoot growth and elongation are inhibited by dinitroaniline herbicide action.

Squashes of treated root tips reveal chromosomes in a characteristic “C” (colchicine)-mitosis or a condensed prometaphase configuration (Figure 3). The chromosomes condense, as in a normal prometaphase, but no metaphase or later mitotic stages are noted. Generally, the number of cells in mitosis is also increased despite the increase in only those cells in mitotic stages up to and including prometaphase (30, 32). With the electron microscope, no microtubules are observed in treated cells. Because there are no spindle microtubules, chromosomes cannot move to the poles of the cell during mitosis. Nuclear membranes re-form after the cell has attempted mitosis, but generally these re-formed nuclei are heavily lobed to accommodate all of the chromosomes (Figure 4). Occasionally, separated groups of microtubules may form micronuclei away from the main clump. These

symptoms have been reported in a variety of plants and for all of the dinitroaniline herbicides examined (3, 8, 20, 30, 32).

The loss of all microtubules explains the swollen root tips typical of dinitroaniline treatment. Cortical microtubules are

Table 1. Microtubule arrays, their roles in cellular processes, and consequences of their loss.

Array	Function(s)	Consequences of loss/alteration
Cortical	Organizing cellulose microfibril deposition and orientation, setting cell shape.	Uneven thickening of walls, isodiametric cells.
Preprophase	Setting plane for subsequent cell division.	? division plane not set.
Spindle and kinetochore	Movement of chromosomes during mitosis.	No chromosome movement; tetraploid, reformed nucleus (generally lobed). Multipolar mitosis.
Phragmoplast	Organizing the new cell plate formation after mitosis.	Incomplete or no cytokinesis, abnormally oriented cell wall.

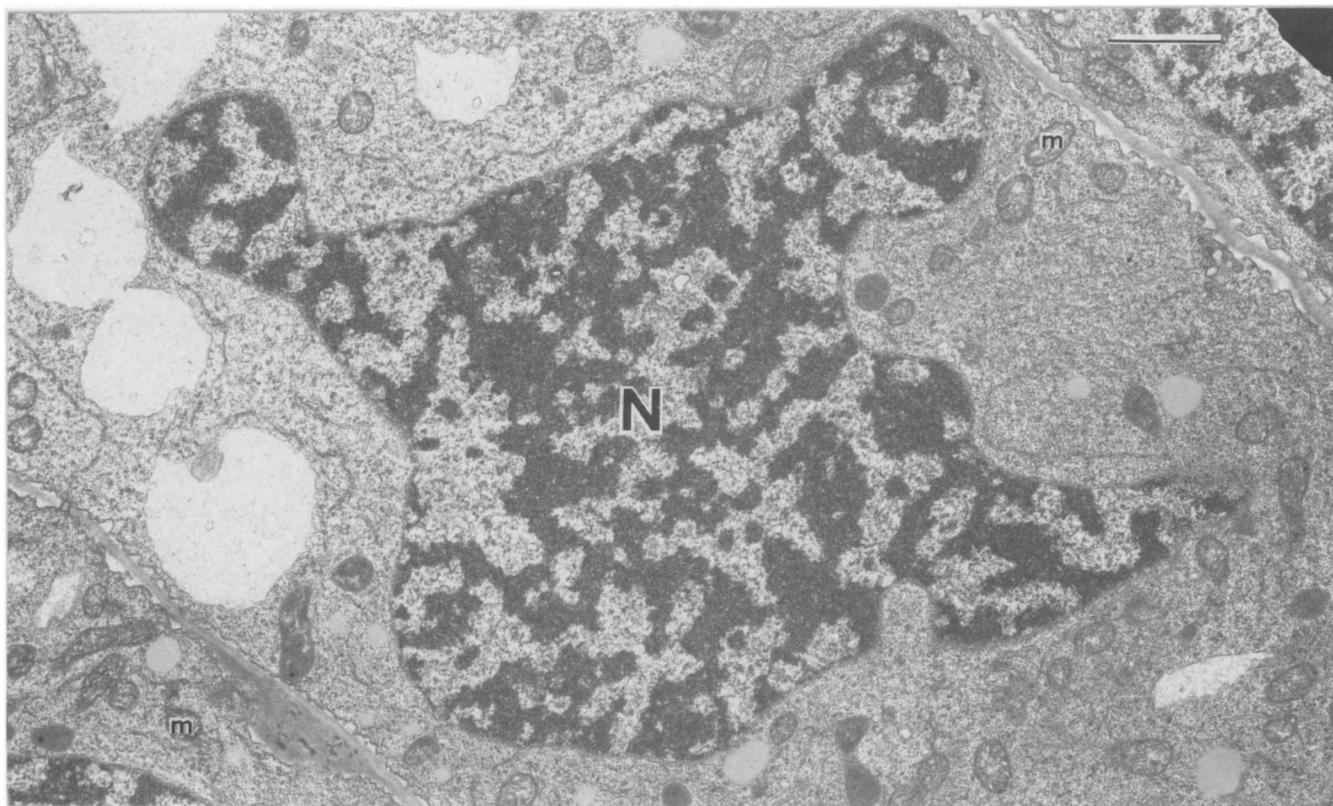


Figure 4. Electron micrograph of a lobed nucleus that is the result of nuclear membrane formation after a condensed prometaphase, such as that shown in Figure 3. N = nucleus; M = mitochondrion; Bar = 2.0 μm .

involved in cell shape (8). Without these microtubules, cells cannot elongate but rather expand isodiametrically (square-shaped, rather than rectangular). Thus, the swollen or club-shaped root tip results from the production of isodiametric cells, because of the loss of cortical microtubules.

Biochemical studies. The data accumulated indicate that dinitroaniline herbicides interact directly with the major microtubule protein tubulin. Direct binding of oryzalin to purified fractions of tubulin from *Chlamydomonas* and rose tissue cultures has been demonstrated, although the binding ratio observed in the two cases is different (9, 20, 24). Tubulin is very susceptible to proteolysis and some of the differences in binding between investigators may be due to proteolytic loss of herbicide binding sites.

Although the exact molecular mechanism is unknown, it is assumed that the dinitroaniline herbicide binds to the tubulin heterodimers in the cytoplasm. As the herbicide-tubulin complex is added to the growing microtubule, further growth of the microtubule ceases. With depolymerization of the microtubule from the “- end” of the tubule, the tubules become shorter and shorter, eventually resulting in a complete loss of microtubules. The most dynamic microtubules are likely to be the most affected if this mechanism is correct, and this is the case. Cortical microtubules are among the most resistant, whereas spindle and phragmoplast microtubules are among the most sensitive (3).

Oryzalin also inhibits the polymerization of tubulin into microtubules *in vitro*. Morejohn et al. (20) were able to inhibit microtubule polymerization even in the presence of the microtubule stabilizer taxol, although the concentrations of herbicide required for complete inhibition were somewhat higher than is required for *in vivo* depolymerization. Vaughn and Vaughan (34) isolated tubulin from the dinitroaniline-resistant and -susceptible biotypes of goosegrass (*Eleusine indica*) and were able to prevent microtubule polymerization in extracts of the susceptible but not the resistant biotype. These *in vitro* polymerization data are the most convincing proof that dinitroaniline herbicides interact directly with tubulin. The extracts used contained nearly pure tubulin and the effects are obtained with dinitroaniline herbicides, but not with other herbicides that cause mitotic disruption without microtubule loss (20, 24, 34). Interestingly, animal tubulin polymerization is unaffected by oryzalin (2, 21), and dinitroaniline herbicides do not disrupt mitosis or microtubules *in vivo* in animal cells. Thus, the inherent differences in animal and plant tubulin have conferred resistance to these classes of microtubule disrupters in animal cells.

Selectivity. Dinitroaniline herbicides are most effective in controlling small-seeded grasses in larger, dicot oil seed crops such as cotton. Hilton and Christiansen (10) found a correlation between the lipid content of seed and the

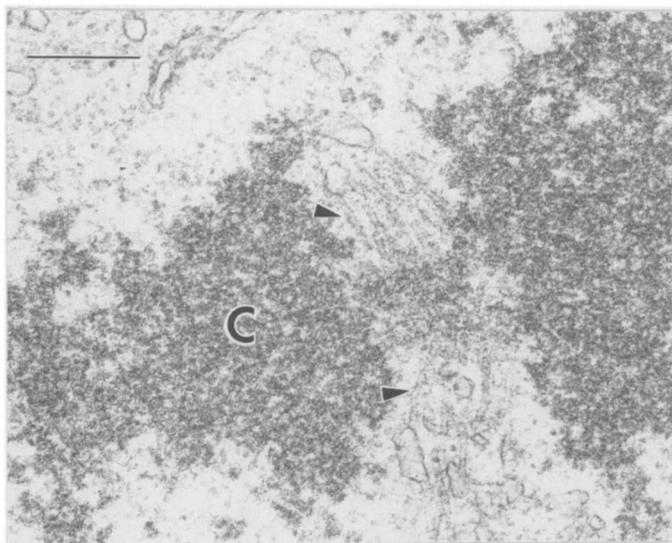


Figure 5. Electron micrograph of a kinetochore tuft (arrows) of microtubules after treatment of onion root tips with pronamide. C = chromosome, Bar = 0.50 μ m.

sensitivity of a plant to trifluralin: the higher the lipid the more tolerant the plant. These authors assumed that the dinitroaniline herbicide would be partitioned into the lipid bodies away from its site of action. These authors also found that coating the seed with oil "safened" the plant from subsequent herbicide damage.

Phosphoric amide herbicides. The phosphoric amide herbicides exert the same effects as the dinitroaniline at the gross morphological and cellular level (25). They have also been shown to bind tubulin and to inhibit the polymerization of tubulin *in vivo* (19). One of the phosphoric amide herbicides, amiprofosmethyl, has been used extensively in investigations of the loss of microtubules from plant cells (e.g. 19). None of these herbicides are marketed commercially in North America.

Pronamide and MON 7200. The herbicide pronamide also causes much of the same symptomology as the dinitroaniline herbicides: arrested or condensed prometaphase figures and root tip swelling (15, 26, 28). Pronamide does cause a slightly different effect, however. At the kinetochore regions of the microtubules, small tufts of microtubules are noted (Figure 5), rather than the complete absence of microtubules characteristic of the phosphoric amide and dinitroaniline herbicides (28). With these short kinetochore microtubules, no meaningful chromosome movement may take place and the net effect is a cell arrested in prometaphase. Secondary effects, such as the lobed nuclei found after dinitroaniline herbicides, are also noted with pronamide.

Pronamide binds to tubulin and can prevent *in vitro* assembly of microtubules (1). The mechanism by which pronamide disrupts microtubule development must be different than the dinitroanilines and phosphoric amide herbicides such that small microtubules rather than no microtubules result. One possible explanation is that binding of pronamide

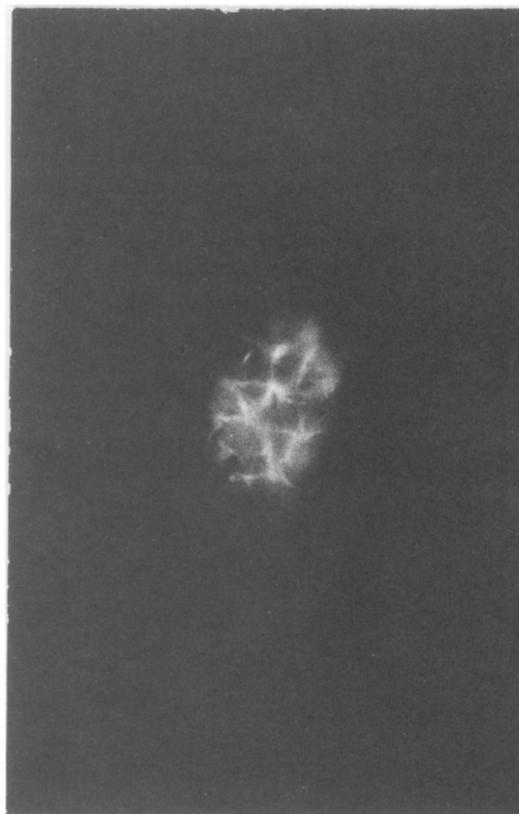


Figure 6. Immunofluorescence micrograph of chlorpropham-treated onion root tips probed with monoclonal anti α -tubulin. Instead of the bipolar spindle characteristic of control cells (Figure 2C), many small spindles are observed. $\times 800$.

to tubulin results in less stable microtubules so that elongation may proceed for a short time. Thus, the short microtubules may be the result of destabilized microtubules due to pronamide.

MON 7200, or dithiopyr, causes much of the same effects as pronamide (13, 17, 18). This compound does not bind to tubulin (18), but rather binds to a protein of about 65 kilodaltons, which is in the molecular weight range of several MAPs recently isolated from higher plants (4). Thus, MON 7200 may interact with a MAP involved in microtubule stability, resulting in shortened microtubules similar to those observed after pronamide treatment.

Carbamate herbicides. Some, but not all, of the carbamate herbicides disrupt mitosis but the mechanism of action of these compounds is unlike the compounds that inhibit microtubule polymerization or destabilize microtubules. At the light microscopic level, these compounds produce multipolar mitotic figures. That is, chromosome movement during anaphase is directed toward three or more foci rather than the two foci of a normal anaphase (7). Similarly, microtubule arrays after treatment with chlorpropham or propham reveal minispindle configurations (Figure 6). After this multipolar division, the nuclear membranes re-form

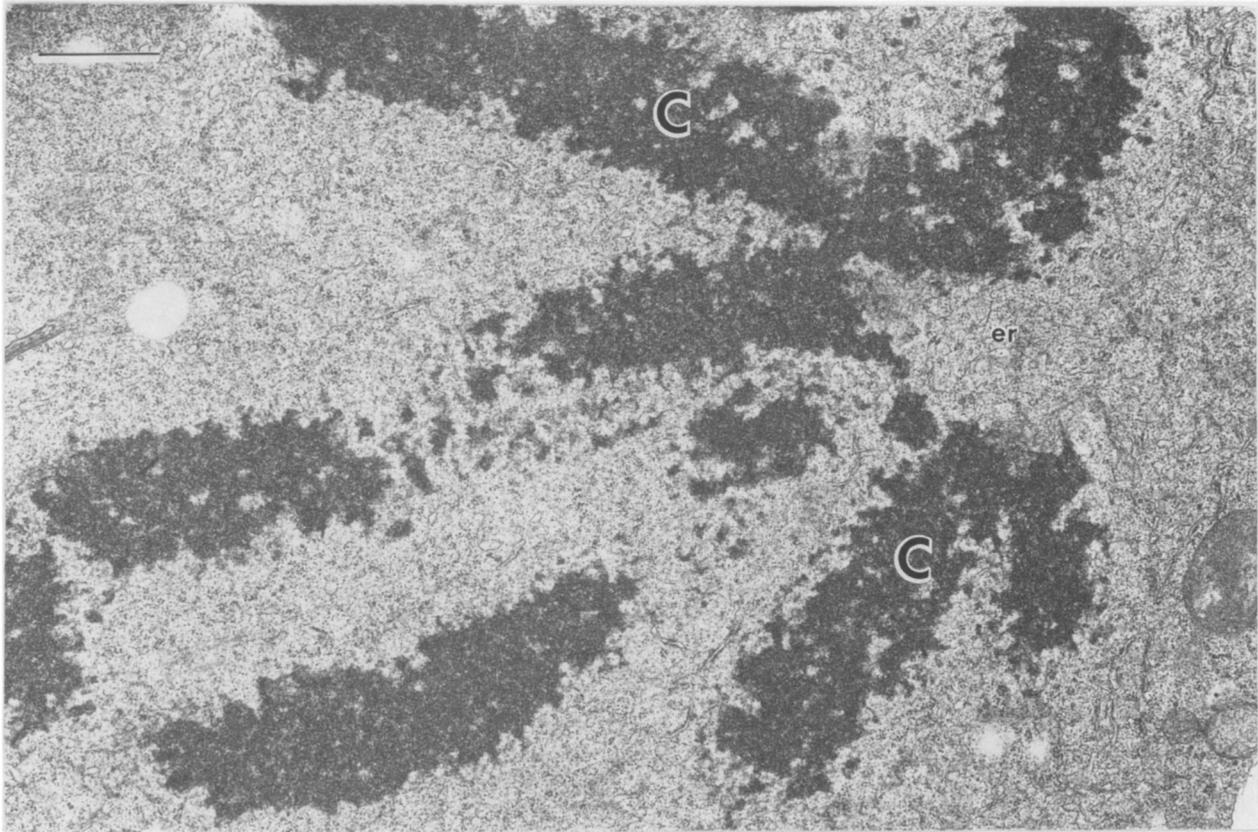


Figure 7. Electron micrograph of a terbutol-treated onion root tip. The chromosomes (C) are gathered together around a zone containing numerous membranes, most likely endoplasmic reticulum (er). Bar = 1.0 μ m.

around the micronuclei, and highly branched and oddly shaped phragmoplast arrays are formed. The abnormal phragmoplasts organize irregularly shaped and abnormal cell walls (8, 27, 32). It is believed that carbamate herbicides disrupt the spindle microtubule organizing centers, fragmenting them throughout the cell. Thus, spindle microtubules may be organized at sites other than the two poles of the cell and chromosomes may move to more than the one pole. The molecular site of action of these compounds is not known, nor are the structures that are involved in this microtubule organization which they disrupt.

As mentioned above, not all of the carbamates cause these effects (26). Barban, propham, chlorpropham, and carbetamide all seem to disrupt mitosis in this manner. None of the thiocarbamates, swep, nor asulam caused any mitotic disruption, resembling the mitotic-disrupting carbamates [(26) and Table 2]. Asulam does cause lagging chromosomes, as noted previously by Sterett and Fretz (23), but none of the multipolar mitosis typical of the others.

Terbutol has been grouped with the carbamate herbicides, but its mechanism of action is distinct from the other carbamates. Instead of the fragmented, multipolar anaphase typical of the other carbamate mitotic disrupters, terbutol actually causes a clustering of the chromosomes (Figure 7).

Table 2. Effects of various carbamate herbicides on mitosis in onion and oat root tips (Lehnen and Vaughn, unpublished). Root tips were treated with concentrations of carbamate up to 1 mM for 24 h. The effects were then monitored by root tip squashes and immunofluorescence microscopy.

Carbamate	Effects on mitosis
Barban	} Multipolar mitosis
Propham	
Chlorpropham	
Terbutol	Star anaphase
EPTC	} None, even at 1 mM
Swep*	
Diallate	
Triallate	} Lagging chromosomes, but no multipolar divisions
Asulam	

*Swep caused substantial growth reduction and, especially at higher concentrations, reduced the mitotic indices to near zero. Mitotic figures that were observed appeared normal, however.

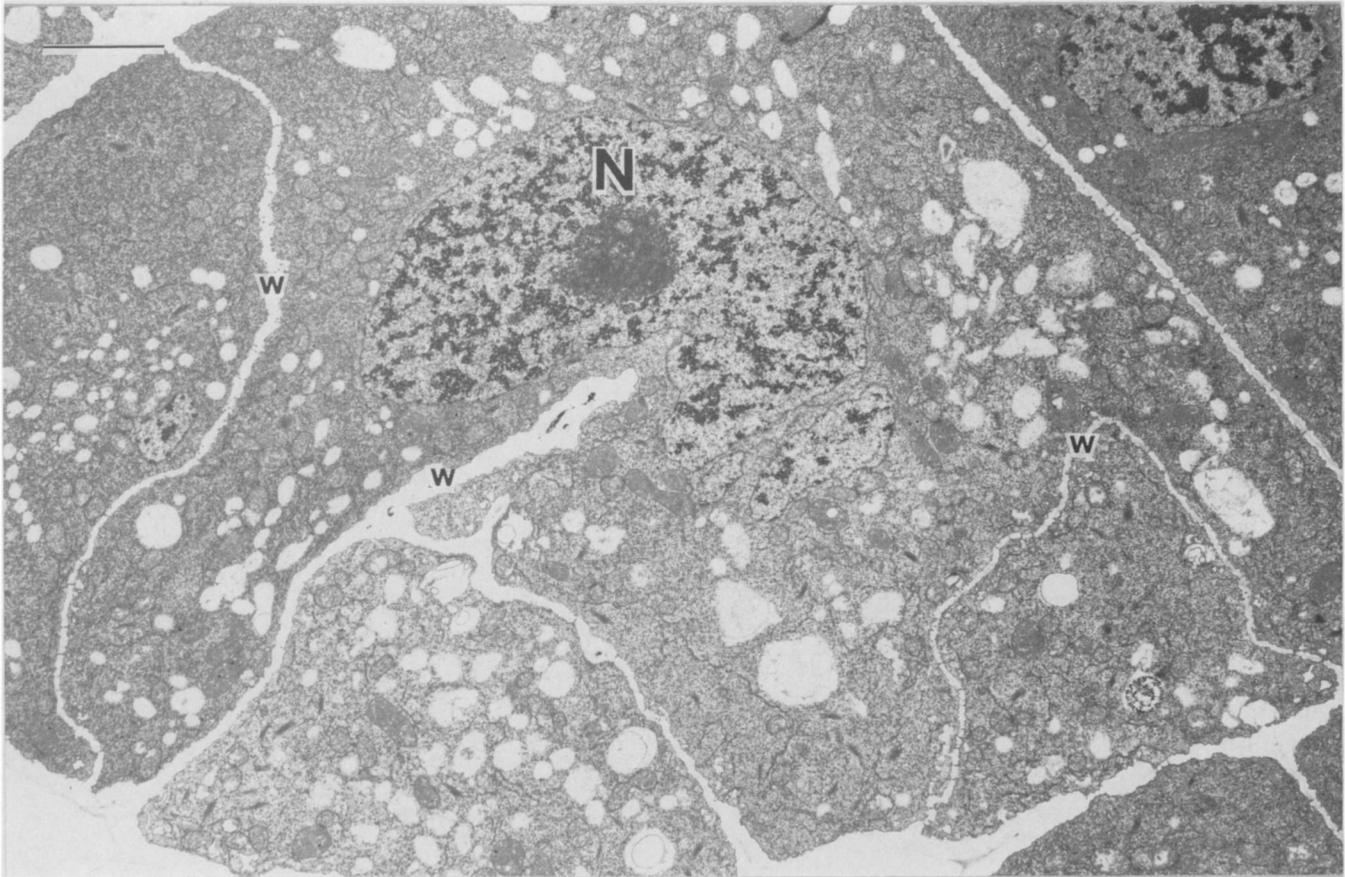


Figure 8. Electron micrograph of a DCPA-treated oat root tip. Note the abnormal cell wall (w) that is the result of abnormal phragmoplast microtubule arrays. N = nucleus, Bar = 2.0 μ m.

They appear drawn into a star-like configuration at their centromeres: a so-called star anaphase figure (14). Immunofluorescence microscopy reveals a clustering of microtubules, emanating from a zone at the center of which the kinetochores are gathered. At this center, the endoplasmic reticulum (ER)³ is concentrated and microtubules seem to have their termini in this mass of ER (Vaughn and Lehen, unpublished). Hepler (6) has speculated that the ER has some role in mitosis, perhaps in sequestering calcium, causing an environment favorable to microtubules nucleation and elongation. Terbutol, which seems to cause an aggregation of the ER, also causes a rearrangement of the microtubules. These data indicate that the ER may be the spindle MTOC in higher plants (6).

DCPA. DCPA is a widely used herbicide for turf grasses and its effects on plant cells have been investigated in a number of laboratories over the years. In most of the studies, cell plate formation has been suggested as the process blocked most effectively by the herbicide (11, 12, 29). In many of the cells, the newly formed cell plate is incomplete or misoriented so that the two nuclei are not separated at mitosis (Figure 8). Oftentimes, the wall will contain loops or be abnormally thick in one portion and thin in another. In the

most severe cases, no wall is formed at all and zones of tissue with multiple nuclei in a common cytoplasm are found (29). Phragmoplast microtubule arrays are abnormally oriented (29) and are found dispersed throughout the cytoplasm rather than restricted to the area set by the preprophase band as the division plane (Lehnen and Vaughn, in preparation). Thus, the primary effect of DCPA seems to be as a disrupter of phragmoplast microtubule organization and production.

Some effects of DCPA are also noted on the mitotic microtubule arrays because some multipolar divisions and arrested prometaphase figures are also noted, especially in the meristematic areas (11, 29). Thus, some of the effects of DCPA are more typical of the other herbicides, although the pronounced effect on phragmoplasts and wall formation may take place even though these other effects may not be noted in the cell. As for the carbamate herbicides, nothing is known of the biochemical mode of action of DCPA.

Conclusions. Herbicides that disrupt mitosis as a primary mechanism of action may be grouped into three divisions: A) those that cause arrested prometaphase figures similar to colchicine, B) those that disrupt spindle microtubule organization, and C) those that disrupt phragmoplast microtubule organization. Group A could be divided into those herbicides

that result in complete microtubule depolymerization, such as oryzalin or amiprofosmethyl, and those with the persistent kinetochore microtubule turfs found in pronamide- and MON 7200-treated cells. However, because the net effect of these compounds is identical, they may be thought of as acting in the same manner. Most of the compounds in group A interact directly with tubulin, as demonstrated by *in vitro* inhibition of polymerization. Compounds in groups B and C do not cause microtubule depolymerization (as shown *in vitro* in one case and *in vivo* by many) and probably interact with the uncharacterized MTOCs of higher plants. Carbamates disperse the MTOCs whereas terbutol aggregates them so that multipolar or star anaphase configuration, respectively, results. DCPA may have several effects on the cell but is most potent as a disrupter of phragmoplast MTOCs.

Studies of the mode of action of mitotic disrupter herbicides allow us to discover the mechanisms by which the herbicide causes its effect. The proteins and processes required for cell division are, in many cases, unknown. For example, the identity of MTOCs in higher plants, either structurally or biochemically, is not known. MAPs have only recently been isolated from higher plants. Herbicides that disrupt mitosis may become useful tools in determining which processes and proteins are critical for mitosis and thus will answer fundamental questions of cell biology.

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