Biologically Active Compounds from Field Fungi

Peter M. Scott and Emmanuel Somers

A wide range of fungal species that attack living plants are known to produce biologically active compounds, some of which have proved human toxicity. Biologically active metabolites from the field fungi are reviewed with particular reference to the genera *Alternaria, Fusarium, Helminthosporium, Phytophthora,* and *Stemphylium.*

Christensen (1965) divided the fungi that invade cereal grains into field fungi, storage fungi, and advanced decay fungi. He defined field fungi as those that invade the grains or kernels before harvest. We have extended this definition to include fungi found on all types of growing plants.

Much attention has been given to the storage fungi such as *Aspergillus* and *Penicillium* species. It is of value to consider the metabolites produced by field fungi, for these could well remain in crops after harvest and after the death of the fungus. The best known example of mycotoxicosis caused by field fungi is ergotism (Barger, 1931).

We have chosen to review the biologically active metabolites of species of *Alternaria, Fusarium, Helminthosporium, Phytophthora,* and *Stemphylium,* selected as representative of fungi that affect growing plants. Like most plant pathogens they can be grown in culture, which is convenient for metabolite production. Biological activity is defined in nearly all cases in terms of toxicity to plants, animals, or microorganisms. Fungal metabolites (excluding those from the higher fungi) that are toxic to animals are commonly referred to as mycotoxins.

ALTERNARIA

Fungi of the genus *Alternaria* are frequently found in grains (Christensen, 1965). *A. solani* causes early blight of tomatoes (Walker, 1967) and can rot the fruit itself. Several species of *Alternaria* are pathogens of citrus fruits (Joly, 1967), and *A. kikuchiana* produces black spot disease of the leaves and fruits of Japanese pears (Sugiyama *et al.,* 1966b). Table I shows that several phytotoxins have been obtained from *A. kikuchiana.* The more recently isolated altenin (Sugiyama *et al.,* 1966a,b) (I) is a faint yellow liquid which also produces a black spot on pear leaves. The phytoalternarins (Hiroe *et al.,* 1958) are crystalline toxins, causing leaf necrosis, but no structures have been proposed.

Another recently isolated phytotoxic metabolite is zinniol (II) (Starratt, 1968) isolated from cultures of *A. zinniae,* a fungus pathogenic to zinnia and other flowers. The compound is toxic to plant seedlings and inhibits germination of seeds (White and Starratt, 1967).

Although *Alternaria* that are toxic to animals are known (Doupnik and Sobers, 1968; Joffe, 1965; Mirocha *et al.,* 1968a), no specific animal toxin has been recorded. Tenuazonic acid (3-acetyl-5-*sec*-butyl-4-hydroxy-3-pyrrolin-2-one) (III) is of interest in that it inhibits growth of human and animal tumors (Shigeura, 1967), and suppresses protein synthesis in Ehrlich ascites and rat liver cells.

Alternariol (IV) from *A. tenuis* is an acetate-malonate-derived aromatic compound and has been synthesized enzymatically (Sjöland and Gatenbeck, 1966). Alternaric acid (V) can be formed in tomato fruits inoculated with *A. solani* (Brian *et al.,* 1952).

FUSARIUM

Fusarium species infect grains (Christensen, 1965; Hewett, 1967), fruit (Wormald, 1955), and vegetable plants such as tomato (Walker, 1967). As early as 1936, *Fusarium graminearum* was shown to produce a toxic principle in barley which killed young pigs (Christensen and Kemkamp, 1936), and the importance of *Fusaria* as toxin producers is apparent from the Russian work (Joffe, 1965) on alimentary toxic aleukia. Two of the principal toxic fungi associated with this disease, *Fusarium sporotrichioides* and *Fusarium poae,* formed steroidal toxins named, respectively, sporofusariogenin and poaefusariogenin (Joffe, 1965). Maximum toxin formation in these fungi took place at low temperatures and at the stage of abundant sporulation.

Table II shows that several other mammalian toxins have been isolated from *Fusarium* species. A recent example is (±)-2-acetamido-2,5-dihydro-5-oxofuran {(±)*N*-(2,5-dihydro-5-oxo-2-furyl)-acetamide} (VI), which is toxic to mice (Yates *et al.,* 1968). Far more toxic is diacetoxyscirpenol (scirpene-3α,4β,15-triol-4,15-diacetate) (VII); the oral LD_{50} in rats is 7.3 mg. per kg. (Brian *et al.,* 1961) and it is also phytotoxic. Diacetoxyscirpenol has also been described under the name anguidin (Loeffler *et al.,* 1964, 1967; Ståhelin *et al.,* 1968). Since it is produced by several species of *Fusarium* in yields as high as 125 mg. per liter of culture (*F. scirpi*) (Brian *et al.,* 1961), more attention should be paid to the natural distribution of this compound in

Food and Drug Directorate, Ottawa, Ontario, Canada

Table I. Biologically Active Metabolites from Alternaria

Metabolite	Species	Active against	References
Altenin[a]	*A. kikuchiana*	Pears	(Sugiyama *et al.*, 1966a,b)
Phytoalternarins A, B, and C	*A. kikuchiana*	Pears	(Hiroe *et al.*, 1958)
Zinniol[a]	*A. zinniae*	Plant seedlings	(Starratt, 1968; White and Starratt, 1967)
Tenuazonic acid[a]	*A. tenuis*	Animal tumors, viruses	(Kaczka *et al.*, 1964; Shigeura, 1967; Shigeura and Gordon, 1963; Stickings, 1959)
Tentoxin[a]	*A. tenuis*	Plants	(Templeton *et al.*, 1967)
Alternariol[a]	*A. tenuis, A. dauci*	Bacteria	(Freeman, 1966; Raistrick *et al.*, 1953)
Alternaric acid[a]	*A. solani*	Plants, fungi	(Bartels-Keith and Grove, 1959; Brian *et al.*, 1949; Grove, 1952)
Alternarine	*A. solani*	Bacteria, fungi	(Darpoux *et al.*, 1950)

[a] Structure known.

plants and feeds. Diacetoxyscirpenol can be detected on thin-layer chromatograms by a concentrated sulfuric acid spray (Gilgan *et al.*, 1966). Two minor metabolites, referred to by melting point, were also obtained by Brian *et al.* (1961). The structure of one of these (m.p. 135–36°), was elucidated by Tidd (1967) as 3α,4,7α,15-tetrahydroxy-scirp-9-en-8-one-4,15-diacetate; it is thus related to diacetoxyscirpenol. Both metabolites were also highly toxic to rats and plants. Another toxin related to diacetoxyscirpenol is T-2 toxin {8-(3-methylbutyryloxy)-scirpene-3α,4β,15-triol-4,15-diacetate} (VIII) (Bamburg *et al.*, 1968b). The LD_{50} in mice was 3.04 mg. per kg. (i.p.) (Yates *et al.*, 1968), and in trout was 6.1 mg. per kg. (Marasas *et al.*, 1967). Systems of nomenclature in this series of toxins have been discussed by Bamburg *et al.* (1968a) and by Godtfredsen *et al.* (1967).

Zearalenone (IX), also known as F-2, is an estrogenic metabolite produced by *Fusarium graminearum* (*Gibberella zeae*) in stored corn (Mirocha *et al.*, 1967). A concentration of 14 p.p.m. was recently found in a hay sample which was implicated in decreased fertility in dairy cattle in England (Mirocha *et al.*, 1968b). It has been synthesized by Girotra and Wendler (1967) and by Taub *et al.* (1967), and increases the rate of growth of lambs (Andrews and Stob, 1965). Further biologically active metabolites of *F. graminearum* remain to be fully characterized; one made swine refuse to eat infected feed and another was emetic (Curtin and Tuite, 1966; Prentice and Dickson, 1968).

Fusaric acid (5-butylpicolinic acid) (X) has been detected in living plants infected by pathogenic *Fusaria* (Singh and Husain, 1964). Studies on the chemical changes undergone by fusaric acid in host plants show that decarboxylation, *N*-methylation, oxidation of the side chain, and probably splitting of the pyridine ring can occur (Gäumann, 1958; Jost, 1965). Decarboxylation in fact would produce a more toxic compound, 3-*n*-butylpyridine (Gäumann, 1958). When projecting the importance of plant pathogen toxins from in vitro studies, in vivo production and stability of the fungal metabolites should be considered.

Enniatins A and B (XI) are between the highly active alternaric acid and much less active fusaric acid in phytotoxicity. In addition, they are antibiotics. Enniatin C is related in structure but almost without antibiotic properties. The three naturally occurring enniatins have been synthesized by Russian and Swiss chemists (Plattner *et al.*, 1963; Ovchinnikov *et al.*, 1964; Quitt *et al.*, 1963; Shemyakin *et al.*, 1963a,b) and are cyclohexadepsipeptides, not cyclotetradepsipeptides as previously supposed. A relation between conformational states of the enniatins and related compounds in solution and their antimicrobial activities has been proposed (Shemyakin *et al.*, 1967).

HELMINTHOSPORIUM

Species of the genus *Helminthosporium* are described under various other generic names, *Cochliobolus*, *Ophiobolus*, and *Pyrenophora*, and are pathogens of cereals, grasses, and other plants. Some of their biologically active metabolites (Table III) have confusing synonyms. The nomenclature of the ophiobolins has recently been sorted out with assignation of new trivial names (Tsuda *et al.*, 1967). Ophiobolin A (XII) has been known as ophiobolin (Nozoe *et al.*, 1965b), cochliobolin (Canonica *et al.*, 1966a), and cochliobolin A (Canonica *et al.*, 1966b). Ophiobolin B (XIII) has even more synonyms: zizanin (Ishibashi, 1962a), ophiobolosin A (Ohkawa and Tamura, 1966), cochliobolin B (Canonica *et al.*, 1966b), and zizanin B (Nozoe *et al.*, 1966). These two closely related metabolites, obtained from several species of *Helminthosporium* in Japan and Italy, are toxic to rice seedlings. Ophiobolin A has been detected in fungally diseased leaves by ultraviolet spectrometry (Oku, 1965). Both compounds are toxic to mice, particularly ophiobolin B, which has an LD_{50} of 4.4 mg. per kg. (i.p.) (Ishibashi, 1962a). No biological data are yet available for ophiobolin C (zizanin A) (XIV) (Nozoe *et al.*, 1966), which is structurally similar to the other ophiobolins. Further compounds in this series are also known (Nozoe *et al.*, 1966; Tsuda *et al.*, 1967).

Pyrenophorin (XV), isolated from *Helminthosporium* (*Pyrenophora*) *avenae* by Ishibashi (1961), was shown by Nozoe *et al.* (1965a) to be identical with the anti-

Table II. Biologically Active Metabolites from Fusarium

Metabolite	Species	Active against	References
Fusariogenins[a]	*F. sporotrichiodes, F. poae*	Animals	(Joffe, 1965)
2-Acetamido-2,5-dihydro-5-oxofuran[a]	*F. equiseti, F. nivale*	Mice, rabbit skin, fungi, bacteria	(White, 1967; Yates *et al.*, 1968)
Diacetoxyscirpenol[a]	*F. tricinctum, F. equiseti*, etc.	Rats, mice, dogs, rabbits, plants, cells	(Bamburg *et al.*, 1968b; Brian *et al.*, 1961; Dawkins, 1966; Sigg *et al.*, 1965; Stähelin *et al.*, 1968)
Deacetylanguidin	*F. concolor*, etc.	Yeasts, tumors	(Loeffler *et al.*, 1964, 1967)
Toxin, m.p. 135–6°[a]	*F. scirpi, Gibberella intricans, F. equiseti*	Rats, plants	(Brian *et al.*, 1961; Tidd, 1967)
Toxin, m.p. 185–8°	*F. scirpi*	Rats, plants	(Brian *et al.*, 1961)
T-2 toxin[a]	*F. nivale, F. tricinctum*	Mice, trout	(Bamburg *et al.*, 1968b; Marasas *et al.*, 1967; Yates *et al.*, 1968)
Nivalenol	*F. nivale*	Mice, cells	(Ohtsubo *et al.*, 1968)
Zearalenone[a]	*F. graminearum*	Swine, rats, mice	(Mirocha *et al.*, 1967, 1968a; Stob *et al.*, 1962; Urry *et al.*, 1966)
Chlamydosporins A and B		Bacteria	(Faivre-Amiot *et al.*, 1952)
Bostrycoidin[a]	*F. solani, F. bostrycoides*	Bacteria	(Arsenault, 1965; Hamilton *et al.*, 1953)
Fusaric acid[a]	*F. oxysporum*, etc.	Plants, fungi, yeasts, bacteria	(Bär, 1963; Gäumann, 1957; Sadasivan, 1961; Singh and Husain, 1964)
Dehydrofusaric acid[a]	*F. lycopersici, Gibberella fujikuroi*	Plants	(Gäumann, 1957)
Javanicin[a]	*F. martii,*	Bacteria, plants	(Kern and Naef-Roth, 1965)
Fusarubin[a]	*F. solani,*	Bacteria, plants	(Kern and Naef-Roth, 1965)
Marticin[a]	*F. solani,*	Plants, bacteria	(Kern and Naef-Roth, 1965)
Isomarticin[a]	*F. javanicum*	Plants, bacteria	(Kern and Naef-Roth, 1965)
Novarubin[a]	*F. martii,*	Fungi, bacteria, plants	(Kern and Naef-Roth, 1967)
Norjavanicin[a]	*F. solani*	Fungi, bacteria, plants	(Kern and Naef-Roth, 1967)
Enniatin A[a]	*F. oxysporum*, etc.	Plants, bacteria, yeasts	(Gäumann *et al.*, 1960; Quitt *et al.*, 1963; Shemyakin *et al.*, 1967)
Enniatin B[a]	*F. oxysporum*, etc.	Plants, bacteria, yeasts	(Gäumann *et al.*, 1960; Plattner *et al.*, 1963; Shemyakin *et al.*, 1967)
Enniatin C[a]	*F. oxysporum*		(Ovchinnikov *et al.*, 1964; Plattner and Nager, 1948; Shemyakin *et al.*, 1967)
Lateritiin II	*F. lateritium*	Bacteria	(Cook *et al.*, 1949; Lacey, 1950)
Avenacein	*F. avenaceum*	Bacteria	(Cook *et al.*, 1949; Lacey, 1950)
Sambucinin	*F. sambucinum*	Bacteria	(Cook *et al.*, 1949; Lacey, 1950; Tirunarayanan and Sirsi, 1961)
Fructigenin	*F. fructigenum*	Bacteria	(Cook *et al.*, 1949; Lacey, 1950)
Oxysporin	*F. oxysporum*	Bacteria	(Tirunarayanan and Sirsi, 1961)
Lycomarasmine[a]	*F. oxysporum, F. lycopersici*	Plants	(Hardegger *et al.*, 1963; Pouteau-Thouvenot and Barbier, 1966)
Culmomarasmin	*F. culmorum*	Tomato	(Kiss *et al.*, 1960)
Lycopersin	*F. lycopersici, F. vasinfectum*	Bacteria	(Kreitman *et al.*, 1950)
Phytolycopersin	*F. oxysporum*	Tomato	(Hiroe and Matsuo, 1965)
Phytonivein	*F. bulbigenum, F. oxysporum*	Watermelon	(Hiroe and Aoe, 1955; Hiroe and Nishimura, 1956)
Fusanins A and B	*F. hyperoxysporum*	Bacteria	(Texera, 1948)
Fusafungine	*F. lateritium*	Microorganisms	(Couchoud, 1958; Servier, 1966)
Fusarinines A,[a] B,[a] and C[a]	*F. roseum, F. cubense*	Arthrobacter	(Diekmann and Zähner, 1967; Sayer and Emery, 1968)
Gibberellins[a]	*Gibberella fujikuroi*	Plants	(Shibata *et al.*, 1964)
Poine	*F. sporotrichiella*	Tumors	(Elpidina, 1959)

[a] Structure known.

Table III. Biologically Active Metabolites from Helminthosporium

Metabolite	Species	Active against	References
Ophiobolin A[a]	*H. oryzae, H. zizaniae, H. turcicum, Ophiobolus heterostrophus, H. leersii, H. panici-miliacei*	Rice seedlings, mice, fungi	(Canonica *et al.*, 1966a; Nozoe *et al.*, 1965b; Oku, 1965; Tsuda *et al.*, 1967)
Ophiobolin B[a]	*H. zizaniae, H. oryzae, Ophiobolus heterostrophus*	Rice seedlings, mice, fungi, bacteria	(Canonica *et al.*, 1966b; Ishibashi, 1962a; Nozoe *et al.*, 1966; Ohkawa and Tamura, 1966; Tsuda *et al.*, 1967)
Ophiobolin C[a]	*H. zizaniae, Ophiobolus heterostrophus*		(Nozoe *et al.*, 1966; Tsuda *et al.*, 1967)
Ophiobolosin B	*H. oryzae*	Rice seedlings, fungi, bacteria	(Ohkawa and Tamura, 1966)
Pyrenophorin[a]	*H. avenae*	Fungi, yeasts	(Ishibashi, 1961; Nozoe *et al.*, 1965a)
Siccanin[a]	*H. siccans*	Fungi	(Hirai *et al.*, 1967; Ishibashi, 1962b)
Helmintin	*H. siccans*	Fungi	(Inagaki, 1962)
Helminthosporal[a]	*H. sativum*	Cereals, fungi	(Spencer *et al.*, 1966)
Helminthosporol[a]	*H. sativum*	Plants	(Kato *et al.*, 1964; Spencer *et al.*, 1966)
Victoxinine	*H. victoriae*	Cereals	(Pringle and Braun, 1960; Pringle and Scheffer, 1964; Scheffer and Pringle, 1963)
Victorin	*H. victoriae*	Oats	(Pringle and Scheffer, 1964; Wheeler and Luke, 1963)
Carbtoxinine	*H. carbonum*	Corn	(Pringle and Scheffer, 1967)
H. carbonum toxin	*H. carbonum*	Corn	(Pringle and Scheffer, 1967)
Cytochalasins A[a] and B[a]	*H. dematioideum*	Cells	(Aldridge *et al.*, 1967; Carter, 1967)

[a] Structure known.

Table IV. Biologically Active Metabolites from Phytophthora

Metabolite	Species	Active against	References
Coumarin[a]	*P. infestans*	Plants, animals	(Austin and Clarke, 1966; Goodwin and Taves, 1950; Hazleton *et al.*, 1956)
Umbelliferone[a]	*P. infestans*	Plants, fish	(Austin and Clarke, 1966; Goodwin and Taves, 1950; Murti and Seshadri, 1947)
Herniarin[a]	*P. infestans*	Fish	(Austin and Clarke, 1966; Murti and Seshadri, 1947)

[a] Structure known.

fungal metabolite isolated in addition to radicinin from *Stemphylium radicinum* by Grove (1964), for which a structure based on half the true molecular weight had been proposed (Aldridge and Grove, 1964). Siccanin (XVI) is yet another antibiotic isolated in Japan (Ishibashi, 1962b) from *Helminthosporium;* it is active against *Trichophyton* species at 0.1 μg. per ml.

Perhaps the most interesting metabolites of *Helminthosporium* species, to the plant pathologist, are two host-specific phytotoxins from *H. victoriae* and *H. carbonum.* Pringle and Scheffer (1964) have reviewed this topic especially with reference to the toxin of *Helminthosporium victoriae,* victorin, which in part consists of a much less potent nonspecific toxin, victoxinine. More recently Pringle and Scheffer (1967) have isolated a host-specific toxin from *Helminthosporium carbonum,* together with a nonspecific toxin analogously named carbtoxinine, though there is yet no evidence that carbtoxinine is a part of the *H. carbonum* toxin molecule.

PHYTOPHTHORA

Phytophthora is a notorious plant pathogen, yet there is little information as to its metabolites. *P. infestans* is the infamous cause of potato late blight, and also causes late blight of tomatoes (Walker, 1967). Other *Phytophthora* species can attack fruit, and as many as 30% of cider apples in England have been rotted by *Phytophthora* in a wet season (Wormald, 1955). To give one more example, the most universal of all cocoa diseases is black pod, caused by *P. palmivora* (Powell and Harris, 1964). Yet the only simple metabolites to be recorded (Table IV) for *Phytophthora* are coumarin (XVII), umbelliferone (7-hydroxycoumarin) (XVIII), and herniarin (7-methoxycoumarin) (XIX), found in small amounts in cultures of *P. infestans* (Austin and Clarke, 1966). Coumarin, and to some extent umbelliferone, depress growth of oat roots (Goodwin and Taves, 1950); coumarin also inhibits germination of radish seeds (Bernhard, 1959).

Table V. Biologically Active Metabolites from Stemphylium

Metabolite	Species	Active against	References
Radicinin[a]	*S. radicinum*	Plants, bacteria	(Clarke *et al.*, 1963; Grove, 1964; Kato *et al.*, 1968; Yokota *et al.*, 1967)
Pyrenophorin[a]	*S. radicinum*	Fungi, yeasts	(Aldridge and Grove, 1964; Nozoe *et al.*, 1965a)
Stemphone	*S. sarcinaeforme*	Chick embryos, zebrafish larvae	(Scott and Lawrence, 1968)

[a] Structure known.

Though certain complex substances, toxic to plants, have also been isolated from *Phytophthora* species in culture (Rönnebeck, 1956; Savel'eva and Vasyukova, 1966), more interest has been shown in production of chemicals by the host plant in response to infection. If a metabolite is not a normal constituent of the plant and is antifungal it is termed a "phytoalexin." One recent example is rishitin (Katsui *et al.*, 1968) obtained from tuber tissues of white potatoes infected by an incompatible race of *P. infestans*. Recent reviews on the subject of abnormal metabolites produced by plants in response to fungal infection include those of Uritani (1967) and Rohringer and Samborski (1967). The phenomenon is not, of course, confined to *Phytophthora* infection. Metabolites harmful to humans and animals may be produced by this process. Ipomeamarone (Akazawa, 1960), a sesquiterpene found in sweet potatoes rotted by *Ceratocystis fimbriata*, is the enantiomorph of ngaione (Denz and Hanger, 1961), a liver toxin from the leaves of the Ngaio tree, and death of cattle has been attributed to the terpenes from bad lots of sweet potatoes (Uritani, 1967).

STEMPHYLIUM

Species of *Stemphylium* occur on forage crops (Renfro *et al.*, 1960), cereal seed (Machacek *et al.*, 1951), tomato plants (Walker, 1967), carrots (Grogan and Snyder, 1952), and other vegetables (U. S. Department of Agriculture, 1960). Very few metabolites from fungi of this genus have been characterized (Table V). Radicinin (XX) is a phytotoxic metabolite of *S. radicinum*, a pathogen of carrots (Grogan and Snyder, 1952). Several structures have been put forward for radicinin (Clarke *et al.*, 1963; Grove, 1964; Yokota *et al.*, 1967), and only recently has Grove's structure been verified by synthesis of (±)-dihydroradicinin (Kato *et al.*, 1968). Radicinin has been patented as an insecticide, herbicide, and plant growth regulator, and has also been obtained from several *Curvularia* species (Yokota *et al.*, 1967). A second metabolite of *S. radicinum* was shown by Nozoe *et al.* (1965a) to be the same as pyrenophorin (XV).

S. sarcinaeforme is pathogenic to red clover (Renfro *et al.*, 1960) and also causes a leaf spot disease of gram in India (Das and Sen Gupta, 1961). The isolation in our laboratory of stemphone (Scott and Lawrence, 1968), a major metabolite of this fungus, marks the first pigment to be characterized for the genus, and apart from the sporogenic substances (P 310's) reported by Trione *et al.* (1966), stemphone is the first metabolite from this species. Evidence obtained so far indicates that it is a *p*-benzoquinone of molecular formula $C_{30}H_{42}O_8$ (Scott and Lawrence, 1968). Stemphone was toxic to 10-day-old chick embryos, zebrafish larvae, and some bacteria.

CONCLUSIONS

Metabolites from fungi infecting living plants, including those with biological activity, could be present in both feeds and the consumers' food. These fungi can be found on the edible parts of plants as well as the leaves and stems, and their metabolites have been shown in some cases to be present in a diseased plant, and may survive after harvest and processing. Some of the compounds mentioned are highly toxic to animals—for example, ophiobolin B and diacetoxyscirpenol and related compounds.

However, nearly all the compounds included in this review have been obtained only in laboratory culture of the fungus concerned. A living plant is a nutritionally different medium, and a fungal metabolite produced in culture may not be present in a host plant. Conversely, metabolites may be produced in the host plant which cannot be obtained in culture. To say whether such metabolites are toxic to animals would require the careful collaboration of plant pathologist, chemist, and toxicologist.

Much more work remains to be done on metabolites of plant pathogenic fungi. A list of common plant diseases gives numerous fungal species on which little or no chemical work is recorded. When one considers how extensively a single species—for example, *Gibberella fujikuroi*—can be studied, the field indeed appears limitless.

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