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 51. G. Dahl and A. Hjort [*Having Herds: Pastoral Herd Growth and Household Economy* (Univ. of Stockholm, Stockholm, 1976)] distinguished "surplus" animals from "fallow herds." Also, dying animals in drought are used for human subsistence.
 52. For example, livestock may be sold during drought by Ethiopian farmers [M. Cross, *New Sci.* (4 April 1985); *ibid.* (14 February 1985)], by Ethiopian shifting cultivators [D. Tuston, *Disasters* 1, 275 (1977)], by Sudanese cultivators [L. Holy, *ibid.* 4, 65 (1980)], and by Kenyan pastoralists [M. O'Leary, *ibid.*, p. 315; R. Hogg, *ibid.*, p. 299], among others.
 53. The following biomass to energy conversions were used: nonwoody plant, 18 MJ/kg (dry weight); wood, 20 MJ/kg (dry weight); animal body, 9.9 MJ/kg (fresh weight); and camel, cattle, and sheep and goat milk, 264, 372, and 406 kJ per 100 ml on average (11). Meat and blood varied according to species and method of preparation (11). Annual mean livestock fresh weights were camel, 405 kg; cattle, 197 kg; donkey, 188 kg; and goat and sheep, 27 kg (17). Energy flows in sales and barter were calculated from commodity prices and energetic conversions as above.
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Conservation Tillage

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Man developed iron and steel tillage tools and animal-drawn implements as he learned to mechanize plant production. In the early 1800's, tillage was shown to benefit crops by providing a suitable seedbed, reducing competition from other plants, improving surface drainage, and changing soil structure.

weeds, and prepare the seedbed. Because of its success, the moldboard plow became a centerpiece of traditional agriculture. Farmers took pride in their straight furrows that buried all traces of the previous crop's residue. This strong tradition has slowed adoption of alternative crop production systems.

Summary. Conservation production systems combine tillage and planting practices to reduce soil erosion and loss of water from farmland. Successful conservation tillage practices depend on the ability of farm managers to integrate sound crop production practices with effective pest management systems. More scientific information is needed to determine the relations between tillage practices and physical, chemical, and biological soil factors that affect plant and pest ecology. There is a need to devise improved pest management strategies for conservation tillage and to better understand the impact of conservation tillage on water quality, especially as it is related to use of agricultural chemicals. While savings in fuel, labor, and soil have induced many farmers to adopt conservation tillage, improved methods and equipment should increase adoption even more.

These findings led to cultural practices that included intensive tillage to optimize crop production. For over 150 years moldboard plowing has been used to incorporate fertilizer and lime, control

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Stubble mulching, a form of conservation tillage, was practiced in the 1930's to control soil erosion by wind. National research efforts to develop stubble mulching systems in the mid-1940's resulted in the development of tillage and planting technology for management of plant residues. Alternative tillage methods did not develop until the mid-1960's, when the introduction of herbicides offered another means to control weeds. At the same time, political and social

concerns about the environment began to surface. Many people considered soil to be one of the most serious pollutants in waterways and worried about loss of soil for food and fiber production. The emphasis in tillage research changed from finding ways to improve the performance of tillage machinery to discovering means to accomplish essential objectives with alternative technology, such as herbicides and crop rotation.

Any tillage practice that reduces soil or water loss when compared to moldboard plowing is considered to be conservation tillage (1). Conservation tillage does not necessarily mean less tillage. In some situations the amount of tillage may be the same as in more conventional practices. Conventional tillage is the use of a moldboard plow for primary tillage followed by implements such as harrows for seedbed preparation. Contouring (planting across the slope) and ridge planting techniques can qualify as conservation tillage. Another conservation tillage method is no-till ("slot" planting), in which special equipment is used to plant seeds in existing vegetation or residues. With no-till, tillage is confined to narrow strips, or slots, which are just wide enough to provide sufficient loose soil to cover the seed. In this article recent developments in conservation tillage are reviewed and research needs relating to pest management and crop development are described.

Purpose of Tillage

The dynamics of tillage have been studied in the United States since the early 1920's. Increased emphasis was placed on tillage research in the early 1950's as crop production and mechanization expanded. Recent concerns about the use of fossil fuels in agriculture brought about new research to increase

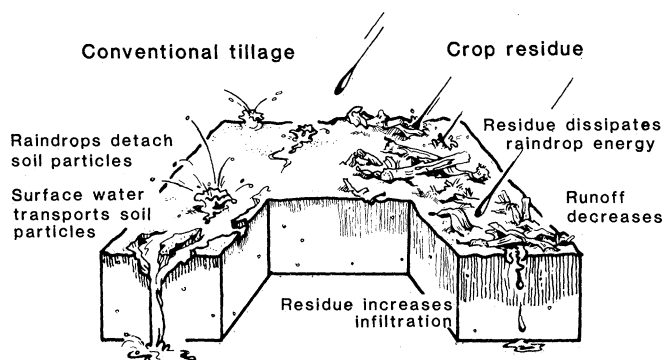


Fig. 1. Effect of conservation tillage on erosion and runoff.

the efficiency of tillage and other crop production operations. Except for grain drying, conventional tillage in nonirrigated production requires more energy than any activity on the farm (2). The covering of plant residues leaves soil susceptible to erosion, and tillage equipment can compact soil, inhibiting root growth (3-6).

The objectives of tillage are:

- 1) To prepare a location and desirable soil structure for seeds and seedlings.
- 2) To control wind and water erosion.
- 3) To control the flow of water, air, and heat into and through the soil.
- 4) To control weeds, insects, and plant diseases.
- 5) To manage crop residue disposition on or in the soil.
- 6) To establish surface configurations such as beds and furrows for irrigation, drainage, and harvest operations.
- 7) To incorporate fertilizers, pesticides, manures, and other amendments.
- 8) To remove foreign materials, such as rocks or roots.

While these objectives are easily defined, expressing the desired conditions in quantitative terms is difficult. Soils react to tillage machinery differently depending on their texture, moisture content, organic matter content, and structure. Because the dynamics of the soil system depends on these properties as well as on weather and the growing plant, determining a specific condition at planting time that will be best for plant

growth and development throughout the growing season is difficult. New electrohydraulic systems to control tillage machinery so that implements can produce desired soil physical conditions are being developed, but criteria for optimum conditions are difficult to specify (7).

Effect of Tillage on Soil Processes

Erosion and runoff. Soil erosion involves detachment and transport of particles and their subsequent deposition. The major transport mechanism is runoff water. Under conventional tillage, the energy of raindrops is dissipated completely by the uncovered surface, resulting in soil detachment, increased surface "sealing," reduced infiltration, and a dramatic increase in runoff (Fig. 1). Erosion rates under these conditions can exceed 100 metric tons per hectare. Under conservation tillage, residue from previous crops serves to buffer raindrop impact. Residues and a rough soil surface maintain higher infiltration rates and reduce runoff. Water that does run off contains less sediment.

Studies of field plots and small watersheds have shown conservation tillage to be highly effective in controlling erosion (8-10). In the Midwest, consistent reduction in soil loss of 75 percent has been achieved with the use of corn residue (11, 12). Even under more erosive practices involving a rotation of corn and

soybeans, conservation tillage can reduce erosion rates by at least 50 percent. Erosion with 30 percent cover can be half that with bare soil. In the erosive Palouse area of the Pacific Northwest, traditional tillage results in erosion rates exceeding 225 metric tons per hectare, but erosion rates of 15 to 20 metric tons per hectare are more common. Intensive residue management and proper timing of tillage can reduce these rates; however, due to a diversity of management techniques, topography, and climate, these high erosion rates have not been reduced to an acceptable level (less than 11 metric tons per hectare).

The benefits of conservation tillage are not limited to reducing erosion brought about by water. In many drier regions of the United States, erosion by wind is a primary cause of soil loss. Crop residues can dissipate wind energy just as they dissipate raindrop energy. Soil erosion by wind for wheat production under conservation tillage is about 2 metric tons per hectare compared to 32 metric tons under conventional systems (12).

Water quality. Runoff water from cropland can contain sediment, dissolved nutrients, and pesticides. In addition to problems caused by its physical deposition, the sediment carries the bulk of the nitrogen (N) and phosphorus (P) loads, as well as adsorbed pesticides and toxic metals. Dissolved nutrients and pesticides, while a small percentage of the total load, are readily available to aquatic weeds and algae and can be the most important indicators of runoff water quality. Reduced soil erosion with conservation tillage is an obvious advantage due to a reduction in sediment and sediment-associated chemical losses (12). However, it must be observed that, although protective residues aid in erosion control, maintaining surface residues can limit management options in the use of fertilizers and pesticides, thus affecting chemical concentrations and losses in runoff. Hence, by using conservation tillage, we may be trading a sediment problem for other contaminants.

Increasing attention has been given to problems of P enrichment of surface waters in the Great Lakes Basin, especially when the effects are manifested as eutrophication. The importance of P in eutrophication is twofold. First, P is often present in surface waters at concentrations that limit algal growth. Second, P inputs to lakes and streams are more subject to control than other nutrient inputs. Whether or not conservation tillage is responsible for increased loads of soluble P in the surface waters depends on how the farming system is managed.

Table 1. Definitions of conservation tillage used in national survey of adoption (29).

Type of conservation tillage*	Treatment during harvest to planting	Width of disturbance over row	Weed control options
No-till or slot planting	None†	2 to 7 cm	Herbicide
Ridge till	None	1/3 of area‡	Combination§
Strip till	None	1/3 of area	Combination
Mulch till	Full width¶	Whole area	Combination

*Conservation tillage is a tillage and planting system that retains at least a 30 percent cover of crop residue on the soil surface after planting. Residue cover may be forage crops, winter cover crops, small grains, or row crops. Reduced tillage, a system not listed, is also a conservation tillage system. †No disturbance. ‡Ridges 10 to 15 cm higher than middle of interrow. Tillage accomplished with sweeps or row cleaners; cultivation used to rebuild ridges. §Herbicide and cultivation combined. ||Tillage in row accomplished with Rototiller, chisel in the row, or row cleaner. ¶Tillage with chisel, field cultivator, disc, sweep, or special blades.

If fertilizer is broadcast and not incorporated into soil, runoff water will have substantially more soluble P (13). If fertilizers are incorporated into soil, actual reductions in the P load are common under conservation tillage (13–15). Fertilizer and other chemical recommendations for wise resource management are often counter to efficient and low-cost farm operation. The evolving technology of conservation tillage is no exception. Innovative methods for applying nutrients are required for compatibility. High-pressure and point injection systems that place nutrients below the residue should be considered. Cases in which high production and enhanced water quality go hand in hand have been found as more is learned about the dynamics of the system. Wisconsin scientists found that corn yields under conservation tillage could be increased by applying fertilizer in the row at planting time. This technique not only resulted in substantial increases in yield, but lower contaminant loads in runoff water compared to those in conventional systems (15).

The most important water quality concern with respect to conservation tillage is increased potential for contamination of surface and ground water by pesticides. By the year 2000, it is expected that conservation tillage will be used on over half of U.S. cropland (16), and conservation tillage systems tend to increase infiltration. Special techniques and different pesticides will be required for sound pest management. Little research has been conducted to find pest management systems that minimize ground-water contamination from agricultural chemicals used in conservation tillage.

Conflicting results have been reported on the effects of conservation tillage on pesticide losses in the runoff and sediment lost from small plots and watersheds. In studies involving small plots, higher losses of pesticides were found under conservation tillage even when runoff volumes were reduced. In other studies of runoff from watersheds, less pesticide loss was reported for conservation tillage than for conventional tillage (13). Models also exist that take into consideration the solubility of chemicals in water and their affinity to eroding soil particles (13). These models show that a reduction in erosion is expected to result in a concomitant reduction in the loss of highly adsorbed pesticide compounds. For compounds that are more water-soluble and less well adsorbed, a reduction in loss will result only through a reduction in runoff—a principal effect of conservation tillage.

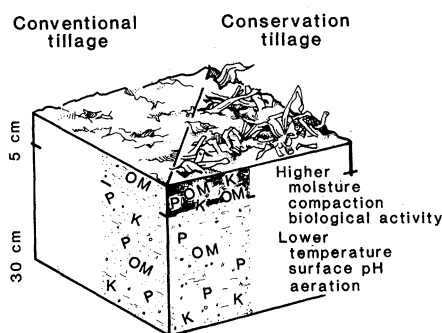


Fig. 2. Effect of conservation tillage on soil properties.

Changes in soil properties. Several investigators have studied the effects of tillage on row-crop productivity (17–21). Trowse (22, 23) found that tillage practices often produce an excellent soil environment for seed germination while ignoring the conditions necessary for optimum root growth at later stages of plant development.

Residues raise the albedo and restrict air movement, resulting in less energy to warm the soil. Since there is less evaporation of soil water and greater infiltration, the thermal conductivity of the soil is greater, dissipating heat to a greater depth and moving heat away from the seed zone. Because the heat capacity of wet soil is greater than that of dry soil, more heat is required to warm the wet, cool soil under the plant residues (24). At typical seed placement depths, soils under conservation tillage can be 3° to 4°C colder than under conventional tillage (25). The soil is usually more compacted (increased bulk density) early in the growing season due to natural subsidence and absence of inversion and fragmentation of the soil from plowing. After several rains the soil in the plow layer (0 to 20 cm) under conventional tillage increases in bulk density, and by season's end may be as dense or more dense than soil under conservation tillage.

The effect of changes in temperature and in other physical properties of the soil on plant growth depends on site-specific conditions. Increased soil moisture is an advantage that commonly increases yields, particularly in those areas that experience water stress during the growing season. Reduced temperature is generally considered a disadvantage in temperate climates, since it can retard early-season growth. Soil compaction produced by tractors and tillage implements often limits yield (22, 23, 26, 27). Thus, whether increased tillage is an advantage or disadvantage for a specific situation is difficult to predict.

Interesting stratification processes are observed under conservation tillage. Fig-

ure 2 shows that organic matter and nutrients such as P and K can accumulate in the upper portion of the soil profile (25). Such accumulation can be partly explained by broadcast application of fertilizer; however, this phenomenon occurs even where fertilizer is not broadcast because the plow layer is not inverted each year. Maximum depth of plant residue incorporation may vary from several centimeters in no-till to 20 cm in moldboard plowing. Stratification can affect soil crusting, water infiltration, seed emergence, viability of weed seeds, pathogen inoculum, insect and other faunal activity, herbicide degradation, and availability of fertilizer nutrients. A redistribution and mixing of fertilizer throughout the soil profile does not occur with some conservation tillage practices. Depending on how the nitrogen fertilizer is managed, lower surface soil pH can occur (Fig. 2). Biological activity in the upper profile of fields under conservation tillage is nearly always greater than in that of fields under conventional tillage. Soil microbes (important to nitrogen transformation) and earthworm population have been shown to increase dramatically (28).

Pest Management

A survey of farmers by the Conservation Tillage Information Center in 1983 revealed that the major obstacles to adoption of conservation tillage were weeds, insects, and diseases (29). Pest control, including cultural and chemical methods, can consume 10 to 30 percent of total farm operating costs. Overall return from use of pesticides is \$4 per \$1 invested (30). Herbicides constituted about 80 percent of the major field and forage crop pesticides used in 1982 (31).

Conservation tillage is being accepted faster than any other practice in the history of farming (32). Whereas such tillage offers advantages, its adoption may create pest problems, some immediately and others as much as 10 years after the change.

Diseases. Fungi and bacteria are principal pathogens associated with surface residues, although viruses and nematodes may also be factors. Leaving crop residues for erosion control is contrary to the traditional practice of burying them to destroy pathogens. However, disease incidence is usually not increased under reduced tillage systems (33), because growers have used foliar-, seed-, and soil-applied fungicides, planted high-quality seed, used disease-resistant varieties, controlled insects and

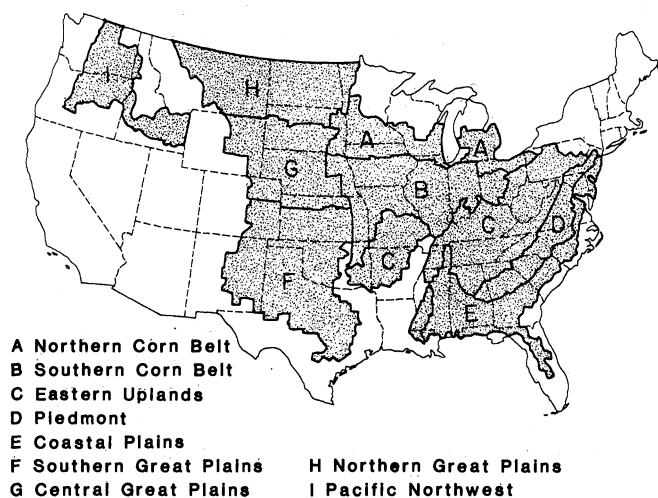


Fig. 3. Tillage management regions in the United States.

weeds, and rotated crops and tillage systems.

A direct relation has been found between the severity of certain plant diseases and the use of conservation tillage (34). Many plant pathogens use crop residues as an overwintering site and a food source. Further research is needed to determine (i) the potential effects of changing tillage practices on the population dynamics of pathogenic and pathogen-antagonistic organisms, (ii) the influence of tillage practices and cropping systems on plant diseases, and (iii) the feasibility of using fungicides or bioagents to kill pathogens in residues or to prevent pathogens from producing reproductive structures thereon.

Insects. Conservation tillage has a variable effect on insect populations depending on the insect species, the tillage system, and the length of time it has been used. Inversion-type tillage to bury crop residues was a traditional sanitation measure for controlling diseases and insects. Deep moldboard plowing destroys overwintering insects, exposes them to weather and birds, and physically prevents or hinders their emergence.

Large amounts of mulch cover and the absence of soil disturbance cause some

increase in above- and belowground insect pests (35). Cooler soil temperatures in the spring delay seed germination, making seed and seedlings susceptible to insects such as wireworms, seed-corn maggots, and seed-corn beetles. The use of prophylactic soil insecticides is difficult if not impossible in some conservation systems. In Colorado, corn rootworms increased after several years of reduced tillage practices, whereas in Oklahoma greenbug aphids decreased where crop residues remained (36, 37).

Further research is needed to determine the effects of tillage practices on the frequency of pest outbreaks and on the composition of insect communities. Since the pest status of insects varies from location to location, such research should be conducted under a wide range of cropping and tillage conditions.

Weeds. Primary and secondary tillage, row-crop cultivation, and other conventional tillage operations are effective in controlling weeds (38). With conservation tillage, herbicides and crop-management strategies are the only means to control weeds.

The effects of weeds on crops remain relatively constant with conventional tillage, but increase dramatically after a few

years with conservation tillage. Perennial weeds are particularly troublesome after only 2 or 3 years of conservation tillage (39), forcing many farmers to return to conventional tillage and some cultivation for control.

Weeds are controlled best in any agroecosystem through integration of plant competition strategies, crop and herbicide rotations, and mechanical methods. In the past 30 years most weed control technology has been developed for conventional tillage systems. Although progress is now being made in developing weed control technology for conservation tillage, weeds still often limit the use of such tillage.

Although herbicides have been used effectively in conservation tillage, other factors associated with weeds and herbicides must be considered in order to make conservation tillage economical and environmentally safe. These factors are (i) the effect of surface crop residues on herbicide adsorption, movement, persistence, and efficacy and on weed seed distribution, viability, and dormancy; (ii) the effect of tillage systems on the population dynamics of perennial and annual weed species; and (iii) the effect on weed control of new chemical, biological, and mechanical application technology; controlled-release herbicide formulations; and new, more species-specific herbicides.

Adoption of Conservation Tillage

The potential for increased crop yields, reduced labor, reduced fuel consumption, and improved control of soil erosion has been a primary factor influencing adoption of conservation tillage. The most limiting factor has been the lack of reliable and economical weed management systems (40).

A national survey of the adoption of conservation tillage was conducted in each county of the United States in 1983

Table 2. Adoption of conservation tillage planting systems in the United States for nonforage crops (29). Values are percentages.

Tillage management region	U.S. cropland	Cropland under conservation tillage	Conservation tillage cropland under					Cropland in summer fallow
			No-till	Ridge till	Strip till	Mulch till	Reduced till	
Pacific Northwest	4.4	22	4.5	2.2		54.5	40.9	26
Northern Great Plains	14.0	23	4.3			69.6	26.1	22
Central Great Plains	8.6	45	6.6	2.2	2.2	53.3	35.5	22
Southern Great Plains	14.9	36	2.8			41.7	52.8	15
Northern Corn Belt	8.6	23	4.3	4.3	1.7	73.9	17.4	
Southern Corn Belt	17.8	38	13.2	2.6		71.1	13.2	
Eastern uplands	5.6	38	36.8			26.3	39.5	
Piedmont	1.4	44	47.7			22.3	31.8	
Coastal Plains	5.3	36	22.2		2.7	36.1	41.6	

(29). Definitions of conservation tillage given in Table 1 were used for this survey. Compilations at the county level were aggregated into tillage management regions (Fig. 3) (41). The tillage management regions were developed to delineate regions in which climate, adapted crops, and farm management would provide some degree of homogeneity in tillage systems (Table 2).

Adoption ranged from 22 percent in the Pacific Northwest to 45 percent in the Piedmont and central Great Plains (Table 2). Partial-width tillage (no-, ridge-, and strip-till) planting systems were used on less than 10 percent of cropland outside the humid and southern tillage management regions, including the eastern uplands and southern Corn Belt. Less than 5 percent of the conservation tillage consisted of no-till in the Pacific Northwest, northern Great Plains, southern Great Plains, and northern Corn Belt. About 7 percent of the central Great Plains was planted under no-till. In the subhumid to humid tillage management regions, use of no-till ranged from 4 percent in the northern regions to 47 percent in the Piedmont (Table 2). No-till was used much less in the Coastal Plains than in the Piedmont and eastern uplands. The natural and traffic-induced soil compaction problem in soils of the Coastal Plains accounts for this dramatic reduction in no-till (42-44). Some strip tillage has been adopted in the central Great Plains, Coastal Plains, and northern Corn Belt.

Mulch tillage, with full-width tillage between harvest and planting, had the highest adoption, ranging from 42 to 70 percent in arid to subhumid tillage management regions (Table 2). Lack of adoption of mulch tillage in the northern Corn Belt compared to the southern Corn Belt (also in the northern Great Plains compared to the central Great Plains) indicates that reduced soil temperatures limit growth as these temperatures approach the limits of crop adaptation (45).

A limited number of adaptable crops explains the low adoption in the two northern tillage management regions that have large amounts of cropland in summer fallow and small grains. These regions account for 76 percent of the cropland in the Pacific Northwest. Growing small grains in a monoculture or a 2-year crop rotation impedes mulch tillage because surface residue harbors inoculum for fungal-type root diseases (46).

Mulch tillage, no-till, and strip till are used for full-season sorghum and corn in the central Great Plains (47-49). The adoption of ridge-till for full-season monoculture of corn and, to a lesser

extent, for monoculture of full-season grain sorghum was already achieved before 1970 (50).

Three distinct cropping systems are found in the southern Great Plains (51). These are (i) grain sorghum, summer fallow, and wheat in the north and west subregion; (ii) a near monoculture of winter wheat (3 of 4 years) in the north and east subregion; and (iii) an area of cotton monoculture with very little use of conservation tillage.

In the northern and southern Corn Belt, the most dominant cropping system is a 2-year corn-soybean rotation. Mulch till is the major conservation tillage practice used in these two systems, with more area planted in corn than in soybeans. In both tillage management regions, ridge till with corn and soybeans is a minor but rapidly growing cropping system.

Conservation tillage is well suited for use in double-cropping systems. Double-cropping is practiced on 7 percent of the cropland in the eastern uplands, Piedmont, and Coastal Plains. Less than 1 percent of the cropland in the central Great Plains and only 3 percent of the cropland in the southern Corn Belt are double-cropped. Winter small grains with no-till soybeans seeded into the grain stubble or grazed winter cover crop is a typical double-cropping system (43, 52-54). The summer crop of corn, grain sorghum, and soybeans is often seeded under no-till. More extensive adoption of no-till for double-cropped soybeans contrasts with much lower adoption of other conservation tillage practices for full-season soybeans. More use of conservation tillage for double-cropped soybeans is partially explained by difficulty in planting full-season soybeans within corn residues. Planting crops into winter cover crops such as small grains, legumes, or grasses using no-till is a popular system in the Piedmont and eastern uplands (8, 55). More strip till is used in the Coastal Plains for double-cropped soybeans than in other tillage management regions because an in-row chisel tool must be operated ahead of the planter unit to alleviate soil compaction. In nearly all instances, small grains or another winter crop are planted after full-width conventional or mulch tillage to avoid soil compaction and poor drainage during winter (56).

Conclusion

The adoption of conservation tillage will have to increase much more in the next 15 years than it has in the past 15

years if greater than 50 percent of U.S. cropland is to be farmed with conservation tillage by the year 2000. Most recommendations coming from research on crop production are based on the soil-plant environment produced by moldboard plowing. We are only now beginning to understand how the soil-plant environment is altered when moldboard plowing is discarded in favor of conservation tillage. It may take 10 years for the full impact of the change to be realized. The ecosystem is certainly changed with respect to temperature and moisture regimes; there may be additional effects on soil compaction, microbial activity, aeration, root growth, and yield. A more complete understanding of these dynamics and the pest ecosystem is important if farm managers are to obtain optimum yields under conservation tillage.

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PERSPECTIVE

Tumor Necrosis Factor (TNF)

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Spontaneous regressions of cancer, rare events but repeatedly recorded, have led generations of investigators to seek explanations for their occurrence and therapeutic maneuvers to increase their frequency. When a number of patients undergoing cancer regression in the late 1800's were found to have concurrent bacterial infections, F. Fehleisen in Germany and William B. Coley in the United States, as well as a small group of other physicians, attempted to induce infections in patients with far advanced cancer. Although antitumor responses were seen, some dramatic, it was difficult to infect most patients, and, when an infection did occur, there was no way to control its severity. Coley, therefore, turned in 1893 to the use of killed bacteria, and the mixture of *Streptococcus pyogenes* and *Serratia marcescens* that he and others used to treat cancer came to be known as Coley's toxins. Coley's work was well known at the time, and in 1934 the American Medical Association stated that Coley's toxins were the only known systemic therapy for cancer. However, with advances in radiotherapy and, subsequently, chemotherapy, clinical interest in toxin therapy diminished, even becoming controversial in certain quarters. Coley's results would have been lost had not his daughter, Helen

Coley Nauts, collected and analyzed the records of her father and other physicians from this country and abroad (1).

In contrast to the eclipse of clinical interest in toxin therapy, laboratory studies of microbial products as antitumor agents have had a long and uninterrupted history. A wide range of microorganisms have been examined, from bacteria, yeast and other fungi to plasmodia and trypanosomes, but most attention has been focused on three groups of organisms: Gram-negative bacteria, mycobacteria such as *Bacillus Calmette-Guérin* (BCG), and corynebacteria such as *Corynebacterium parvum*. One of the most dramatic and reproducible phenomena in experimental tumor biology is the hemorrhagic necrosis of certain mouse tumors that can be seen shortly after the injection of filtrates from cultures of Gram-negative bacteria. Murray Shear and his colleagues at the National Cancer Institute identified the active principle as a polysaccharide (2), and subsequent work showed that this component, also known as endotoxin or bacterial pyrogen, is a lipopolysaccharide (LPS) and a major constituent of the cell wall of Gram-negative bacteria.

Clinical applications of Shear's findings were limited because LPS was considered to be too toxic in humans. BCG and *C. parvum*, however, were subjected to extensive tests in cancer patients, with generally disappointing results. The

clinical use of BCG and *C. parvum* was based on a large series of animal studies, starting with the demonstration by Baruj Benacerraf and myself that BCG-infected mice showed heightened resistance to challenge with transplantable tumors (3). It was generally considered that the action of LPS and BCG was indirect and mediated by the host. In the case of LPS, Glenn Algire of the National Cancer Institute suggested that tumor hemorrhagic necrosis was secondary to LPS-induced hypotension and collapse of tumor vasculature. The systemic antitumor effect of BCG and agents with similar activity was thought to be due to a general augmentation of immunological reactivity, since BCG-infected mice were more resistant to bacterial and viral challenge, rejected incompatible skin grafts more rapidly, and produced higher titers of serum antibody. For many years there has been speculation that macrophages play a key role in the antitumor activity of microbial products. Both LPS and BCG have profound effects on macrophages, activating them to become more phagocytic and more bactericidal. In addition, activated macrophages have the capacity to inhibit or destroy cancer cells in vitro through a variety of mechanisms, including the production of active oxygen intermediates (4).

The discovery of tumor necrosis factor (TNF) provided a clue as to how these diverse reactions to microbial products might be linked. It was during an investigation of the antitumor activity of normal serum, particularly the leukemia inhibitory activity of serum, that we found TNF (5). In attempts to modify the level of antitumor factors in the blood, we tested serum from mice injected with BCG, LPS, or both agents together. The serum of BCG-infected mice injected with LPS (but not serum from mice injected with either agent alone) caused hemorrhagic necrosis of an LPS-sensi-

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