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Farmacology

Johns Hopkins researchers are investigating a troubling potential source of resistant pathogens: the American farm.

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Ellen Silbergeld, Eng '72 (PhD), recalls that she did not want to go to the seminar. She was a professor of epidemiology at the University of Maryland School of Medicine in 1999 when her department's chairman needed an audience for the seminar's presenter, a candidate for a faculty position. Silbergeld recalls the chairman saying, "Please, just sit in the room. You can come to lunch." So she sat in the room, and something caught her attention. The seminar was on hospital-acquired infections, but the presenter mentioned in passing that some drug-resistant infections came from food. That seemed odd. Silbergeld knew you could pick up Salmonella from, say, tainted chicken salad. But how would that Salmonella have become resistant to antibiotics? She turned to a colleague and asked. Because, he said, factory chicken farms routinely feed antibiotics to their flocks, to accelerate growth, and the drugs generate resistance.

Ten years later, Silbergeld, now a professor of environmental health sciences at the Bloomberg School of Public Health, is one of several researchers at Johns Hopkins and around the world assembling evidence that the industrial farming of chickens, pigs, and cattle is cultivating more than poultry and livestock — it's cultivating bacteria that medicine is losing the ability to fight. Antimicrobial drugs, including antibiotics like penicillin, ciprofloxacin, and methicillin, kill pathogenic bacteria. But they simultaneously drive the resistance that is bacteria's defense, especially when administered in low, subtherapeutic doses. Scientists estimate that 50 percent to 80 percent of all antimicrobials in the United States are not used by doctors to treat sick people or animals but are added to farm animal feed, mostly in such subtherapeutic dosages. Public health researchers like Silbergeld are convinced that this nontherapeutic use of antimicrobials is building dangerous genetic reservoirs of resistance. If they are right, industrial agriculture is fostering and dispersing drug-resistant bacteria that impair medicine's ability to protect the public from them.

The United States Department of Agriculture (USDA) estimates that livestock and poultry produce 335 million tons of manure per year, which is one way resistant pathogens get out of animals and into the environment. That's 40 times as much fecal waste as humans produce annually. Farms use it for fertilizer and collect it in sheds and manure lagoons, but those containment measures do not prevent infectious microbes from getting into the air, soil, and water. They can be transported off the farms by the animals themselves, houseflies, farm trucks, and farm workers, and by spreading manure on other fields. Out in the environment, they form a sort of bank of genetic material that enables the spread of resistance.

"This development of drug resistance scares the hell out of me," says Kellogg Schwab. Kellogg Schwab, director of the Johns Hopkins Center for Water and Health, refers to a typical pig farm manure lagoon that he sampled. "There were 10 million E. coli per liter [of sampled waste]. Ten million. And you have a hundred million liters in some of those pits. So you can have trillions of bacteria present, of which 89 percent are resistant to drugs. That's a massive amount that in a rain event can contaminate the environment."

He adds, "This development of drug resistance scares the hell out of me. If we continue on and we lose the ability to fight these microorganisms, a robust, healthy individual has a chance of dying, where before we would be able to prevent that death." Schwab says that if he tried, he could not build a better incubator of resistant pathogens than a factory farm. He, Silbergeld, and others assert that the level of danger has yet to be widely acknowledged. Says Schwab, "It's not appreciated until it's your mother, or your son, or you trying to fight off an infection that will not go away because the last mechanism to fight it has been usurped by someone putting it into a pig or a chicken."

Industrial agriculture, known variously as factory farming, concentrated-animal feeding operations (CAFOs), and industrial farm animal production (IFAP), has produced an abundance of affordable steaks, pork chops, and broilers for grocery shelves over the last 65 years or so. It grew out of chicken farms on the Delmarva Peninsula, Midwestern pork processing plants, and cattle feedlots in Kansas and elsewhere. In 2008, the Pew Charitable Trusts and the Bloomberg School produced a report titled "Putting Meat on the Table: Industrial Farm Animal Production in America," that outlined how, after the conclusion of the Second World War in 1945, farm mechanization and the Green Revolution's program of genetic selection, irrigation, and chemical fertilizers combined to produce grain, soybean, and especially corn harvests of extraordinary abundance. With all that available corn, if you could feed it to livestock, you didn't need to raise animals in pastures. You could concentrate them in barns or feedlots and raise far more animals on far less land.

Meanwhile, starting with mechanized hog slaughterhouses and Delmarva chicken farms, canny entrepreneurs began to figure out how to take traditional animal husbandry — grazing cattle, rooting pigs, and chickens pecking in a barnyard — and transform it into the industrial production of protein, with the efficiencies and economies of scale of any manufacturing industry. They also grasped the entrepreneurial advantages of vertical integration. On Maryland's Eastern Shore, Arthur W. Perdue left his job as a railroad agent in 1920 to sell eggs. By the 1940s, the company he founded began moving into the production of broilers. Arthur's son, Frank, took over the company in 1950 and invested in hatcheries, soybean refineries, feed mills, and processing plants, launching the company on a course to become a modern integrated farming operation. The concept was simple: If Perdue owned the hatchery, the feed production, and the processing plants, it could gain significant efficiencies, control its costs, establish the steady, predictable production of raw materials, and grow into a very large company with control of a significant share of the market. According to Perdue, by 2007 it was processing 633 million chickens per year and had total sales of $4.1 billion.

In July 1946, the Journal of Biological Chemistry published a research paper out of the University of Wisconsin that detailed the results of feeding three antimicrobials to chickens. The summary included a crucial sentence: "Sulfasuxidine and streptomycin singly or in combination lead to increased growth responses in chicks receiving our basal diet supplemented with adequate amounts of folic acid." That is, feeding antimicrobials to chickens made them grow faster. Agribusiness, eager to increase profits by minimizing how long it took to get a chicken breast or pork roast from the farm to your dinner table, was about to become a major customer for pharmaceutical products.

How major is disputed. In 1999, the Animal Health Institute (AHI), a trade association representing 17 companies including Abbott Laboratories, Bayer, Dow AgroSciences, Monsanto Company, and Pfizer, released a study that estimated 17.8 million pounds of antimicrobials were used each year, for all purposes and for all animals, including pets. For its 2001 report, "Hogging It: Estimates of Antimicrobial Abuse in Livestock," the Union of Concerned Scientists (UCS) mined data on antimicrobial production and concluded that AHI's figures were much too low; UCS estimated that 24.6 million pounds are applied annually just for nontherapeutic purposes — primarily growth promotion — in only three types of farm animals — cattle, swine, and poultry. A 2003 paper published by Poultry Science questioned both figures and stated, "No unbiased estimates of antimicrobial use in animals exist at the present time." Any estimate becomes problematic as soon as one understands what UCS called "the dismal absence of information" about both production and consumption of antimicrobials. The federal government does not collect figures on how much product comes out of the pharmaceutical industry, nor does it require agricultural corporations to disclose how much they use.

Bloomberg School researchers sample the air for pathogens in a Delmarva chicken barn.

Photo courtesy

Kellogg Schwab

In his 1945 Nobel Prize address, Alexander Fleming warned that it was easy to produce microbes resistant to his discovery, penicillin: Simply expose them to concentrations of the drug insufficient to kill them. Possibly the first warning that antibiotics could produce drug-resistant pathogens in poultry came as far back as 1951, when two bacteriologists at the University of California, Davis named Mortimer P. Starr and Donald M. Reynolds published a paper that noted in its summary: "The use of streptomycin as a growth-promoting supplement in turkey poults results in the appearance within three days of streptomycin-resistant coliform bacteria." But little apparent attention was paid to Starr and Reynolds, or to Fleming. During ensuing decades, tens of millions of pounds of tetracycline, penicillin, and other antibiotics were fed to animals on American and European farms. In some cases, the drugs were used to treat sick animals, in amounts that killed the bacteria. But most were fed to cattle, pigs, turkeys, and chickens in exactly the subtherapeutic dosages that Fleming warned would only make bacteria stronger.

After Silbergeld first heard about farmers feeding antibiotic additives to broiler chickens, she asked two faculty members in Maryland's poultry science program to show her the school's chicken barns on the Eastern Shore. As soon as she walked into one, she thought, "This is really serious." There were thousands of chickens crowded in tight confines. She says, "They are raised — how can I put this nicely? — they are raised on top of their own shit. They walk around on litter, which is sawdust or some kind of substrate, covered in feces. It's the most unhygienic thing you can imagine." The air was hot and full of dust. Periodic partial removal of litter from the barns created large piles of manure that were stored outside with minimal containment measures. Any farm worker laboring in such a facility had to be exposed to microbes, Silbergeld thought. If the chickens had been fed antibiotics, then some of those microbes had to be drug resistant.

While still at the University of Maryland, Silbergeld decided her first farm project would be to study whether poultry workers and people in farm communities were at risk of carrying the same strains of drug-resistant bacteria found in chickens, a study she finished after she came to Johns Hopkins in 2001. In Eastern Shore communities like Pocomoke City, Princess Anne, Smyrna, and Salisbury, she enrolled three groups of subjects: workers whose job was to catch chickens in the barns to load onto trucks for transport to processing plants, chicken hangers who attached live birds to the mechanized line at the plant, and community residents who did not work in the industry but lived near it. She found that 41 percent of the chicken catchers had been colonized by Campylobacter jejuni, which is commensal in poultry — it derives benefit from the chicken without harming it — but pathogenic in people, where it's the second-leading cause of gastrointestinal disease in the United States. Among the workers at the poultry processing plant, the rate of colonization was 63 percent. Of the nine people who lived near but did not work in the industry, 100 percent had been colonized.

Carole and Frank Morison became contract growers for Perdue 22 years ago on a farm near Pocomoke City. Drive down U.S. 13 toward the Morisons' place and you will see the land become flat as a plank and ideal for farming. The roads around Pocomoke City lead past one chicken farm after another, each marked by a sign displaying the name of the farm and the company that provides its chickens: Aydelotte Farm — Tyson; Sheep House Farm — Tyson; Poor Boy Farm — Mountaire; Meatball Farm — Tyson. You will see long, closed barns vented by giant fans. What you will not see anywhere is a chicken. They are there, hundreds of thousands of them, but they are all enclosed in the barns. From the road, you don't even hear a cluck.

The Morisons began to notice how often their farm neighbors complained of not feeling well. In 1987, Frank Morison, a second-generation Eastern Shore farmer, approached Perdue to get into the chicken business. There was no such thing as becoming a poultry farmer by simply buying some chickens to raise. If you did not have a contract with a processor like Perdue, Tyson, or Mountaire, you would have great difficulty buying chicks, buying feed, or finding a place to sell your broilers after they'd reached market weight. Basically, Morison says, anything but doing business with a big processor was impossible. So Morison borrowed $200,000 against his house and his land to build a pair of 20,000-square-foot barns. Perdue specified every aspect of the construction.

After the barns were built, one day a truck pulled up to the farm and delivered 54,400 chicks, plus the feed that Morison, by stipulation of his contract with Perdue, was to feed them. Perdue dictated the number and type of chicks, which they owned and merely consigned to Morison; the amount, price, and composition of feed; and the date, 51 to 53 days later, on which workers would be back to pick up the grown birds for processing. Whenever the chickens from his farm were processed, Perdue informed Morison how much they weighed, how much it would pay him per pound, and how much the company was deducting for feed and other supplies it had required him to use. Morison says in the end he typically cleared 2 percent to 3 percent per flock, not counting his labor.

Neither federal nor state regulations require processors to divulge the exact contents of the feed they furnish their growers; the government allows the processors to treat that information as proprietary. So the Morisons say they never knew the quantity of heavy metals like selenium, copper, arsenic, and zinc, or the amount of drugs like tetracycline and penicillin, that were going into, and eventually coming out of, the birds on their farm. But they began to notice how often their farm neighbors complained of not feeling well. Carole says, "There are a lot of sarcastic jokes among farmers. You'd be talking to someone and he'd say, 'Yeah, I'm not feeling too good this week, I got vaccinated along with the chickens.' It was just a routine thing. But people were having 'the bug' too often. Kind of like flu symptoms: achy body, upset stomach, bronchial issues." The Morisons exhibited the same symptoms. Around 1995, Carole recalls, she became intolerant of antibiotics, which began to give her hives, upset her stomach, and worsen her asthma. "To this day, I still have problems."

Last July, the Morisons got out of the chicken business. They say that Perdue had notified them that to continue growing for the company, they would need to make $150,000 worth of upgrades to their facilities. They balked at the expense and decided they'd had enough of farming. They are now employed by the Socially Responsible Agriculture Project, working to link farmers all over the Chesapeake Bay watershed and create local markets and local distribution systems. "Going back to raising food the way it used to be raised," Carole says.

At Hopkins, Silbergeld decided to concentrate her initial research on the occupational health aspects of factory farming. With five co-authors from the Bloomberg School and the School of Medicine, she published the first U.S.-based study of poultry workers colonized by resistant microbes, reporting that 50 percent of surveyed workers carried E. coli that was resistant to the antimicrobial gentamicin, compared to only 3 percent of community members who did not work with poultry. She studied the association between occupational contact with live chickens, Campylobacter jejuni, and peripheral neuropathy, and found a significantly elevated presence of anti-Campylobacter antibodies in poultry workers, indicating colonization; many of those workers also reported symptoms of neurological disorders associated with the pathogen.

Photo courtesy

Kellogg Schwab

Researchers at other institutions around the world reported similar associations. At industrial poultry or swine farms, there were drug-resistant bacteria colonizing farm workers and their families. In 2003 and 2004, Kellogg Schwab sampled the air at a factory farm that housed 3,000 hogs in two buildings. The samples contained enterococci, staph, and streptococci, and 98 percent of the bacterial isolates were resistant to two or more common antimicrobials. In a paper published in Environmental Health Perspectives, Schwab suggested that one way bacteria could travel from animals to humans was by workers breathing that air. In another study from 2002 to 2004, Schwab sampled surface and ground water upgradient and downgradient from a pig farm. He and his co-researchers found the downgradient water — that is, water in the direction of flow from the pig barns — contained 17 times as much enterococci, 11 times as much E. coli, and 33 times as much fecal coliforms as water upgradient from the facility. The downgradient pathogens also were much more likely to be antibiotic resistant.

One day, a Bloomberg School colleague down the hall from Silbergeld came back from a weekend on the Eastern Shore complaining about how disgusting she'd found having to drive behind a truck hauling chickens to a processing plant. Silbergeld remarks, "When somebody says 'disgusting,' I say, 'Wait a minute, there's got to be something going on here.'" She and two of her students, Ana Rule and Sean Evans, designed what they called the "baby-you-can-drive-my-car" study. They loaded passenger cars with sampling equipment, figured out that an intersection on the Eastern Shore near the Virginia border would have a lot of poultry trucks passing through on the way to Perdue and Tyson processing plants, and drove to an adjacent shopping center parking lot. Whenever a poultry truck stopped at the traffic light, the researchers would slide in behind and follow it to the processors. Afterward, they sampled the air inside the car, as well as the car's exterior door handles and an unopened soda can they had placed in the car's cup holder. They found that the air in the car and both surfaces showed increased levels of enterococci after they'd driven behind the chicken trucks. Samples obtained before the car followed the trucks contained no resistant enterococci; a quarter of the bacteria isolated after the trucks showed resistance to antimicrobials, including tetracycline, erythromycin, and streptomycin.

This was not the only study that involved a car. Jay Graham, formerly one of Silbergeld's grad students and now at the United States Agency for International Development, was studying issues of waste disposal on the Eastern Shore. He noticed that every time he came back to Baltimore, his car was covered with flies, and this led him to wonder if flies might be capable of dispersing resistant bacteria from factory farms. Graham told Silbergeld that he wanted to do a study. "I said, 'That's OK, so long as you don't bring any flies here.' The next thing I knew, we had these two big jars full of flies in the lab and I thought, 'So much for that.'" Graham had trapped the flies near poultry farms on the Eastern Shore and found resistant staph and enterococci on them. He analyzed both pathogens for drug-resistance genes and found matches in bacteria taken from the flies and bacteria taken from farm litter, a strong indication that flies are a potential source of exposure to the resistant bacteria lurking in farm wastes.

Scientists know that resistant pathogens can travel from farms by air, water, bird, housefly, chicken truck, or manure spreader, but they do not yet have a good answer to how far they can travel or how long they can remain viable. Just because a researcher detects drug-resistant staph in an air sample doesn't prove it's likely to make anyone sick. But one means of transmission that can cover significant distances is person-to-person — a farm worker, for example, picks up bacteria in a chicken barn and passes it to a family member, who passes it to a member of the community, who brings it into a health clinic or hospital, where it takes up residence and begins causing antibiotic-resistant infections in surgical patients and the immuno-compromised. For years, scientists, physicians, and the public have regarded increasingly prevalent drug-resistant infections as a hospital problem (see "Bugs vs. Drugs," Johns Hopkins Magazine, February 2008). That's where dangerous microbes like vancomycin-resistant enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA) lurk and spread. But then hospitals began to report more and more people who had never been near a health care facility coming through their doors already colonized by resistant bacteria. Where were people picking up bugs like MRSA, which now kills more than 20,000 people each year, more people than die from AIDS?

About three years ago, Silbergeld began thinking about MRSA and industrial agriculture. She was not the only one. In November 2006, Dutch researchers reported the case of a young mother treated for mastitis in October 2004. Cultures taken by her general practitioner revealed MRSA, which was then found in her husband and baby daughter. Her husband was a farmer with 8,000 pigs, and when researchers tested 10 chosen at random from the farm, they found genetically identical MRSA in eight of them, and the same bug in three other workers from the farm. In another case, also from Holland, a 63-year-old woman had been admitted to a hospital with MRSA-caused endocarditis. When scientists typed her infection, they found it did not match hospital-acquired strains of MRSA, nor the strains causing community-acquired MRSA skin infections in the United States. What it did match was MRSA isolated from Dutch pig farms. Yet another study from Holland found the rate of MRSA colonization among pig farmers to be 760 times that of the general public. A year later, Canadian research published in Veterinary Microbiology was the first to find MRSA in North American pigs and pig farmers; scientists studied farms in Ontario and found MRSA in 25 percent of tested pigs, and 20 percent of workers from farms that had colonized animals. On farms that were free of colonized pigs, there were no human cases. Finally, last January, a study out of the University of Iowa sampled 299 pigs and 20 workers from two farms in Iowa and Illinois. The researchers found MRSA in 49 percent of the animals and 45 percent of the people. This was the first such finding in the United States, and the strain, ST398, was identical to what had been found in Canada and Holland.

About three years ago, Silbergeld began thinking about MRSA and industrial agriculture. Silbergeld has begun a MRSA study of her own, trying to establish attributable risk — that is, how much exposure to industrial agriculture contributes to the overall prevalence of MRSA in people coming into hospitals. The crux of the matter, she believes, comes down to molecular biology. Bacteria have a remarkable capability for sharing genes, through what is known as horizontal gene transfer. The old view of resistance was Darwinian: In the presence of antibiotics, a mutation would be naturally selected if the mutated gene helped a microbe survive application of the drugs. "That underestimates the brilliance of microbes," Silbergeld says. Molecular biologists now understand that within a microbial community, one microbe can acquire genetic material from another microbe, even a microbe of a much different type, then incorporate it in its own genome and thus acquire resistance to an antibiotic it has not yet even encountered. It's as if bacteria are capable of downloading resistance from a gene database.

What's more, microbes carry genes in what are called resistance cassettes, which can be thought of as kits that contain a variety of genes for fighting off different drugs. So, a germ resistant to tetracycline may have a resistance cassette that contains not only the gene for fighting off that drug, but genes resistant to other drugs, as well. The result? A person could be colonized by a tetracycline-resistant germ that does her no harm, but lurks in her system and contains, in its cassette, resistance to methicillin. If this unlucky person then acquires a simple staph infection, and that staph encounters the first microbe and taps its resistance cassette, her routine staph infection has now become MRSA and she could be in real trouble. Silbergeld's biggest concern is that factory farms are building reservoirs of these resistance cassettes in animals, in the environment, and in humans.

The trade association for the Eastern Shore's poultry producers is Delmarva Poultry Industry, Inc. The day before Earth Day 2009, the headline on DPI's Web site read, "Every Day is Earth Day for Delmarva's Chicken Industry." The agriculture industry argues that removing antibiotics will result in more sick animals, that there is insufficient data to prove that resistant pathogens from farms are making people sick, and that there needs to be better drug-specific risk assessment. For its part, Perdue states that it does not use antibiotics for growth promotion, "nor do we use any antibiotics continuously for any reason," according to a statement on its Web site. In a 2006 USA Today story, Tyson's chief veterinarian said that his company had reduced its antibiotic use from 853,000 pounds in 1997 to 59,000 pounds in 2004, and now applied antibiotics to less than 1 percent of its broilers. (A Perdue spokesperson said the company would not consent to an interview for this story. Neither Tyson nor DPI returned calls from Johns Hopkins Magazine.)

The May 2009 issue of For the Record, "straight talk about antibiotic use," published by Alpharma Animal Health, a division of King Pharmaceuticals, cites four studies that state the risk of transmission of drug-resistant pathogens from farm animals to humans is negligible, as would be the benefit of withdrawing antibiotics such as virginiamycin from agricultural use. Three of the studies were conducted by Cox Associates, a consulting firm that does health-risk analysis for the USDA and for a variety of corporations and industry associations, including the American Petroleum Institute, the Chemical Manufacturer's Association, Monsanto, and Mobil Oil. One Cox study, published in Environment International, says that "it appears very probable that such a withdrawal [of virginiamycin from agricultural use] would cause many times more human illnesses than it would prevent." That study acknowledges use of a quantitative assessment tool that was developed with financial support from AHI, the agricultural pharmaceutical trade association.

Photo by Dale Keiger Liz Wagstrom, assistant vice president of science and technology for the National Pork Board, disputes the premise — she calls it "a kind of urban legend" — that subtherapeutic dosages of antibiotics drive resistance. She says, "When you go out looking for hard data, you can find examples where that may be true, and you can find examples where that's not demonstrated. So the fact that subtherapeutic use is automatically going to be more selective for resistance than any other use of antibiotics — I'm not sure that I'm willing to say that that's a hard and fast rule."

Wagstrom makes a similar argument in regard to MRSA: "There's been a lot of fingers pointed at the potential contribution of pigs to the U.S. epidemic of MRSA, and it's been based on very little data. I think it's been positioned to try to put fear in people about modern agricultural practices, and that's probably not scientifically justified."

Defenders of industrial agriculture cite studies from Purdue University, Ohio State University, and Iowa State University that found no proof linking MRSA in pigs to the pathogen in humans, that pigs reared without antibiotics are more likely to carry Salmonella and parasitic disease, and that 96 percent of antibiotic resistance should be attributed to human, not agricultural, use of drugs.

The National Pork Producers Council's communications director, Dave Warner, says, "We don't believe we are the main cause of antibiotic resistance. The American Veterinary Medicine Association says that on a per-pound basis people and their pets use 10 times as much antibiotics as livestock production does. Every bathroom and kitchen in America has antibacterial soap in it."

He adds, "We are not saying, 'There is no connection, leave us alone.' We certainly are concerned about it. But I don't think that use of antibiotics in livestock ought to be singled out, and if we do something about that all the problems are taken care of. But that's probably an easier problem to go after. There are only 67,000 pork producers [in the U.S.]. How many doctors are out there? And how many people?"

The whole debate exasperates Silbergeld, who says, "These are feed additives. It's like using antibiotics as hair dye." She adds, "We have this practice of permitting the addition of almost any antibiotic that you can think of to animal feed, for no therapeutic purpose, under conditions that absolutely favor the rise of resistance. We have no controls or management of the wastes. Our food safety system is a shambles. This is a situation that is widely recognized by the World Health Organization, the American Medical Association, and by others, and nothing happens! It's astounding to me!"

Silbergeld and Schwab support the use of drugs to treat sick animals but believe all antibiotics should be banned from animal feeds. They have followed the debate over cefquinome, a fourth-generation cephalosporin antibiotic. A Delaware company, InterVet Inc., wants FDA approval to use cefquinome to treat bovine respiratory disease. But the antibiotic is chemically related to cefepime, one of the few remaining options for treating deadly infections in cancer patients. Scientists fear that if pathogens develop resistance to cefquinome, that resistance could quickly ruin cefepime for human use. The American Medical Association, several other health groups, and the FDA's own advisory group have all urged the agency to reject the drug for use on farm animals, but it has yet to do so. Silbergeld is appalled.

"Sometimes I think we're such a dumb species, we don't deserve to survive on this planet," she says. "I mean, how many times do we have to do this?"

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