Two ears of corn, two bushels of potatoes, two pigs, two calves, two chickens, two turkeys now grow where but one grew before. This has been achieved through the concerned work of many people in all walks of science and farming.

Among the several scientific discoveries which substantially contributed to the abundant yields of our meat, egg and milk production was the astonishing discovery in the early 1950's of the "antibiotic growth effect" on livestock. It was at first unexpected, illogical, and baffling, but enormously exciting for it opened new vistas of research in animal science.

"Great scientific discoveries result from the exposure of a natural phenomenon to an enquiring mind," said Louis Pasteur, and so it was with the whole field of antibiotics commencing with the discovery of penicillin, the now familiar wonder drug.

Thousands of bacteriologists often had seen the blue mold Penicillium, contaminating their isolation plates and rendering them tainted and useless. They, too, had seen the blank (inhibition) areas around the growing molds where the bacteria failed to grow.

Yet it took the genius of an Alexander Fleming to recognize, in 1928, that the mold must be producing a substance which prevented the bacterium from growing—in fact, an "antibiotic".

It took a decade, however, before this laboratory curiosity found practical application in disease control and another five years before it could be produced in sufficient quantity to be available to all at low cost. In time, incidentally, to save thousands of lives in World War II.

Robert H. White-Stevens is Chairman, Bureau of Conservation and Environmental Science, Cook College, Rutgers University, The State University of New Jersey, New Brunswick.
The antibiotic era was born with Fleming's discovery, and the search began for other natural compounds with antigerm activity that also were safe at effective doses for use on man and the higher animals—livestock and pets.

In 1944 the soil microbiologist Selman Waksman and his associates, at the New Jersey Agricultural Experiment Station, isolated Streptomycin from a soil organism, Streptomyces griseus. This antibiotic was found to be active against a wide array of bacterial diseases of both humans and livestock. The most significant is the tuberculosis organism—a world-wide plague which has scourged mankind and man's domestic animals for centuries.

Later Waksman and his co-workers, in 1949, isolated a group of three antibiotics, again from a related soil mold—Streptomyces fradiae, which he named the Neomycins. These also revealed activity against certain skin diseases of humans and livestock.

Benjamin Duggar, in 1948, after 40 years of research and teaching at the experiment stations in Missouri and Wisconsin, discovered with his co-workers at the Lederle Laboratories of the American Cyanamid Company the first of what became a series of extraordinarily effective antibiotics for both human and veterinary medicine—chlorotetracycline (Aureomycin®)—from the soil mold Streptomyces aureofaciens, a yellow pigmented fungus.

Interestingly, the sample of soil from which Duggar isolated this particular mold came from the Missouri Agricultural Experiment Station.

The next discovery was oxytetracycline (Terramycin®), found by Finlay and associates at Pfizer Inc. Next came tetracycline (Achromycin®), developed first by Boothe and co-workers at Lederle Labs in 1953 by chemical modification of chlorotetracycline, and later in 1959 by isolation from another soil mold by Heinesmann and associates at Bristol Labs. Inc. Finally, demethylchlorotetracycline (Declomycin®) was prepared by McCormick and co-workers at the Lederle Labs in 1957, again chemically from chlorotetracycline.

Of these four tetracycline antibiotics, chloretetracycline and oxytetracycline have become most generally used in veterinary medicine and farm livestock, although tetracycline also is gaining increased usage. They all possess a broad scope of activity against many important diseases which induce skin, intestinal or general systemic infections.

Because of their stability in formulations, their breadth of spectrum, their activity throughout the body systems of animals,
and their extraordinarily wide margin of safety, these tetracycline antibiotics quickly gained favor among the veterinarians and became the treatment of choice for a wide range of acute and chronic disease problems in livestock production.

In the ensuing years a number of other antibiotics have been discovered and developed for specific and various applications in agriculture.

**High Quality Meats**

During the 1940's a sharp rise in the general income of Americans created an increased demand for high quality meats in our diet.

Intensive research at many experiment stations had revealed the nutrient components essential for animal diets and how these could be combined and fed to achieve rapid growth and efficient production. Essential vitamins, minerals and certain amino acids (the building blocks of all proteins) were identified as to the kinds, the right quantities, and the best combination needed for the various stages of growth and product formation, as in milk, eggs, and meat. This was worked out for chickens, turkeys, pigs, sheep, beef and dairy cattle.

There was, however, one exception—an unknown growth and reproduction factor found in animal protein, but not in plant protein. This factor was required by all single stomach animals, such as the rat, dog, chicken, turkey, and pig but not the multi-stomach animals or ruminants, such as sheep and cattle. Apparently, then, ruminants were capable of producing their own "animal protein factor" (APF). It also had been shown in New Zealand and Australia that multi-stomach animals did, however,
require vegetation grown on soils containing the metal cobalt.

All single stomach livestock had, therefore, to be fed a source of APF or they would rapidly become anemic and their reproduction would fail. Such animal protein sources were supplied from meat scrap, fish meal, and byproducts of the dairy industry. As consumer demand for meat rose, the need for these animal protein byproducts soared.

Through the 1940’s an intensive search was pressed for alternate, cheaper sources of APF. It was found to be present in animal manures, even in processed municipal sludge. This implied APF was actually not an animal protein factor but was produced by various “bugs” living in the intestinal tract.

Then Mary Shorb of the Maryland Station found a bacterium (Lactobacillus lactis) which also required APF to grow, and thus provided a rapid laboratory screening and assay tool to look for possible APF sources. The search quickly accelerated into a race.

Coincident with this research but quite independently, medical researchers for years had been seeking a dietary control for pernicious anemia, an often fatal disease in humans in which the body is incapable of making sufficient blood. The search had been narrowed down to unknown components present in animal livers (for example, beef and pork livers), and injectable liver extracts from these sources had been prepared to aid in controlling this fatal disease.

In 1948 all the various lines of investigation suddenly coalesced, when a dark red crystalline substance was isolated from animal livers and found to contain the metal cobalt. The compound was named “cyanocobalamine” or vitamin B₁₂, and was quickly identified as both the anti-pernicious-anemia factor for humans and the animal protein factor (APF) for single stomach livestock.

Now it was clear why ruminants did not require APF in their diets: the numerous “bugs” in their rumens could make it provided that cobalt was present in their forage.

This Vitamin B₁₂, an extraordinary compound, is active biologically at a few parts per billion in animals and man.

With the discovery of vitamin B₁₂, it became feasible to raise swine and poultry exclusively on plant protein diets—corn and soya plus minerals and vitamins. The search then began for cheap available sources of vitamin B₁₂ for the feed trade. As it had been found to be fermented by various “bugs” (microflora), could the
fermentation residues from the production of antibiotics from molds be a source?

56 Percent Better Growth

Jukes and co-workers at Lederle Laboratories assayed the residues of chlortetracycline (Aureomycin®) fermentation. Vitamin B₁₂ was indeed found to be present in the discarded cake. When a liver extract (vitamin B₁₂) supplement was fed to chicks on a vegetable diet, they grew 19 per cent more in 25 days than the controls. While on the antibiotic residue containing vitamin B₁₂, they grew 56 per cent better than the controls, giving an added growth of 37 per cent more on the fermented residue than from vitamin B₁₂ alone.

The experiment was repeated, and again an increase of 36 per cent over that directly attributable to vitamin B₁₂ alone was observed.

From what did this increased growth arise? Although the fermentation had been extracted for the antibiotic, it was found that about two grams of the chlortetracycline still remained in each pound of dried fermentation residue.

A few quick experiments on purified diets soon established beyond dispute that the antibiotic was indeed the factor which had induced the extraordinary increased growth.

Field trials immediately were initiated on chickens, turkeys, pigs, calves and sheep at experiment stations all over the United States, Canada and later in several European countries. The gathered results were even more spectacular than those first observed in the relatively hygienic laboratory animal rooms.

It seemed that the more exposed the test animals were to stress, adverse climate, and disease the greater became the improvement in growth, livability and feed conversion induced by the antibiotic in their diet.

Experiment station researchers began to test other antibiotics besides chlortetracycline—such as oxytetracycline, penicillin, streptomycin and bacitracin, and later erythromycin and tylosin—at low levels (2 to 10 grams per ton) in the rations of livestock, particularly of young rapidly growing animals.

Some differences were observed in the gains over controls for the various species of animals tested, and under the wide range of conditions tested. But in general a significant promotion in growth and feed conversion was reported.
Within two years of the initial laboratory discovery, a large number of livestock in the United States and Canada were being fed antibiotic supplements at least during the early stages of growth. Unexplained questions that remained however were: What precisely is the role of antibiotics in growth promotion of young animals? And what makes it work?

Even today, after 25 years, scientists cannot completely answer these questions.

For many years nutritionists and physiologists believed that intestinal "bugs" of diverse species were essential for adequate diet digestion among all animals, including humans. Although it had long been established that such a joint relationship is essential for multi-stomach animals such as cattle, sheep and goats, doubts remained as to whether single-stomach animals (pigs, dogs, cats, rats, birds, etc.) and humans really did require such an intestinal population of helpful little creatures for their growth, maintenance and reproduction.

Early experiments designed to prove that certain intestinal organisms were in fact essential—by feeding known bacterial killers, such as sulfa drugs, to rats—produced uncertain results. For in some instances, the treated animals grew more rapidly and appeared healthier than the untreated controls.

In any case the concept of feeding livestock a suppressor of its intestinal "bugs", except in cases of known identifiable disease, was not encouraged for general farm livestock. It was in fact seriously frowned upon by some veterinarians.

**Debate Rages**

The sudden popularity of the practice of feeding antibiotics understandably initiated intensive debate among animal scientists. This was particularly the case at the time as there was really no reasonable, logical rationale to do so, other than the very practical justification that it worked, it promoted growth, it improved appearance, it reduced early mortality and morbidity (disease), and it returned to the grower a substantial savings.

That economic advantage quickly found its way into consumer markets as prices declined and quality improved. Consequently demand rose sharply, particularly for broilers, frying chickens, and turkeys.

But the question of mechanisms of action remained unanswered. Then workers both in England and the United States independently made an astonishingly but really quite reasonable
discovery. Rats, mice and chicks (and later, also, pigs), when grown under absolute sterile conditions, did not show the growth effect when fed such antibiotic supplements. The obvious implication was that this occurred due to the suppression of injurious or at least deleterious intestinal organisms.

Actually, earlier experiments had shown that germ-free animals grew as much as 50 per cent more rapidly than "controls" held in conventional quarters where normal "bug" populations were invariably present.

The mechanism of the antibiotic growth effect was then, at least in part, due to reduction of undesirable organisms. This also explains the abundant evidence from many stations which showed that thanks to low level diet supplementation with antibiotics, the animal could get more mileage out of its ration.

Many field trials revealed that among young rapidly growing, highly susceptible animals, antibiotics significantly reduced such diseases as scours in young calves, dysentery in baby pigs, toxic enteritis in lambs, and "mushy chick" disease in newly hatched chicks.

It was observed, however, that the beneficial effects of low level (2 to 10 grams per ton) feeding of antibiotics tended to wane as the animal grew, though often the initial advantage could still be noted at market.

At first it was concluded that the harmful bugs had become resistant, and therefore the efficacy of the antibiotic was dissipated. This was, in fact, to be expected. However, it was not the case. For new young animals set out in uncleaned quarters, previously occupied, and fed the low levels of antibiotics promptly revealed the customary growth effect.

It was finally recognized that all young animals consume much larger feed intakes per unit of body weight than do older animals. Thus if the antibiotic were to be increased in the diet so that the antibiotic intake per unit of body weight remained virtually constant, as the animal grew, then its effect would continue to be exerted until the animal went to market.

Laboratory and field trials again were set up at experiment stations in various states, in Canada and in England, and levels of antibiotics were fed from 10 to 400 grams per ton at both continuous constant levels and at rates that increased as the test animals grew.

Those antibiotics which are readily absorbed from the intestines (for example, the tetracyclines) yielded spectacular results. Not
Researchers have found that lambs can be removed from their mothers soon after birth and successfully reared on liquid milk replacer diets that include antibiotics.

only were the acute diseases prevented, but also those low grade infections usually present in massed flocks and herds which previously had been an expected sequel to the various unavoidable stress to which all livestock is exposed (vaccinations, dehorning, debeaking, sudden heat or cold spells, wet litter, transportation, etc.).

Thus outbreaks of such “stress” diseases as shipping fever, foot
rot, chronic respiratory disease and various forms of enteritis were effectively quelled.

With these developments, substantial changes in management procedures evolved.

Before the general use of antibiotics in feeds and drinking water, animal groups had been kept small. This was because it had long been recognized that large groups of massed livestock inevitably encourage outbreaks of serious disease which generate excessive mortality and costly sickness among the survivors. Lost feed conversion and increased days to market could readily become ruinous.

**Broiler Flocks of 40,000**

With the introduction of antibiotic feed supplements fed to prevent the outbreak of such diseases, more animals could be housed safely together and more groups could be held simultaneously on the same farm or feed lot. Flocks of broilers were promptly increased, from 3,000 to 5,000 to upwards of 20,000 to 40,000 within the same house. Cattle on feed lots were increased from a few hundred to tens of thousands.

The economics in labor, overhead, and “turn around” time substantially reduced the cost of production, which quickly became reflected in reduced prices to the consumer.

To manage such immense groups of livestock, continuous disease prevention rather than treatment became mandatory. Antibiotics, along with vaccination procedures to immunize livestock against virulent virus diseases, rendered such mass production of livestock practicable and economically sound. This also was the case with other feed medicaments such as coccidiostats to prevent coccidiosis in poultry, and anthelmintics to prevent worm and parasite infestations.

To attempt to treat diseased chickens individually from a flock of 25,000 was obviously quite impracticable. At times it becomes necessary to provide a treatment to control a sudden outbreak of disease, and this generally is attempted by applying the treatment either in the feed or water, or, occasionally, through the air with aerosolized medicine.

However, among such massed animals those which need treatment the most get the least. Those which need it the least get the most, due to the inevitable inability of sick animals to stand up to the competition at the feeders and waterers.

With larger animals such as pigs, sheep and cattle, it is possible
to isolate the sick animals. However, this requires special facilities, considerable labor and professional help. In any case, the disease probably has started already in the apparently healthy animals, which in turn also will require individual treatment.

The grower is fortunate under such dire circumstances if he can retrieve his investment, without profit.

In addition, meat inspection regulations at the dressing and packing plants have become increasingly stringent in recent years. This is largely because the introduction of preventative antibiotic and other medicament feeding of livestock has shown how clean animals can be raised virtually free of disease.

These increased standards, directed primarily at maintaining public health, make it impossible for the producer of livestock intended for marketable meat to remain in business unless he can proceed under a production program first of massed flocks or herds, and second of almost total disease prevention.

If either of these procedures are withdrawn, the predictable result will be a substantial decline in overall meat production efficiency and a sharp and ruinous rise in meat prices to the consumer.

The mechanism of the antibiotic growth effect is, then, the suppression of deleterious micro-organisms. Some of these exert only competition for nutrients. Others coincidentally produce poisons that impair growth efficiency. Still others elicit low grade or chronic disease that can under certain unfavorable conditions burst into fierce disease. And, finally, a fourth group can readily invade massed animal groups and induce serious mortality.

In a sense all animals and, presumably, living things all suffer from infective disease all the time. Those animals fed antibiotics continuously in their diet merely sustain a much lower level of disease from a reduced array of organisms. They therefore respond better in terms of overall growth efficiency.

Resistance Question Raised

Since the use of antibiotics in farm livestock feeding began, the question has been raised repeatedly as to possible development of bacterial resistance to the particular antibiotics used. This was fully anticipated. Monitoring studies were initiated at several stations to determine whether it was actually occurring and, if so, whether it would indicate the ultimate decline of the antibiotic effect.

By the middle of the 1950's such a decline was observed at
some stations where antibiotic feeding studies had been underway for several years. The curious fact developed, however, that the reduction in the observed antibiotic growth effect was not due to slower growth of the treated animals but to a rise in the growth rate of the untreated controls.

Apparently the continuous use of antibiotic-supplemented feeds in the surroundings had reduced the overall level of unfavorable germs to the point that even the untreated animals showed improved growth. However, when all antibiotics were removed from these particular environments, in a relatively short time the overall growth efficiency declined and the antibiotic growth effect could be demonstrated once again.

A survey of the use of antibiotics in livestock feeding reveals that the effect of growth efficiency has been sustained in all areas studied for over 20 years.

The feeding of antibiotics to livestock, at least at registered levels, does not sterilize the intestines or the bodies of the recipient animals. Therefore a considerable number of bugs of many species survive. These obviously are inherently “resistant” to the antibiotic used at the dose level fed.

Yet they do not constitute a threat or hazard either to the particular animal species, to other species within the same environment, to humans who attend them, to those who slaughter, dress or process the meat, or to the consumer of the edible product.

It must be obvious that if the efficacy of antibiotic feeding to livestock had really subsided to the point where it had become ineffective due to resistant organisms, the industry—pressed, as it is with mounting costs—would swiftly abandon the practice.

In 1960 a new discovery, made first in Japan and later confirmed in Europe and the United States, created a fresh concept and concern over the use of antibiotics in the feed of farm animals.

It had been noted that certain strains of a disease organism causing dysentery in man (Shigella) had developed considerable resistance to virtually all drugs previously employed for its treatment, including several antibiotics. This resistance could not be accounted for by the normal course of selection and evolution.

The discovery was made that certain strains of common intestinal bacteria, which themselves usually are not serious disease inducers, can “infect” their multiple drug resistance characteristics into drug-susceptible organisms that induce intestinal dis-
ease, simultaneously rendering them also resistant to the several
drugs.

These "infective" drug-resistant bacteria apparently possess a
Resistant Transfer Factor (RTF) which enables them to transfer
their multiple drug resistance even to essentially unrelated species.
That astonishing property instantly excited the interest of many
scientists, including of course physicians, veterinarians, nutri-
tionists, and livestock researchers.

Review by the British

In England it generated considerable excitement, and a Com-
mittee was authorized by Parliament—the Swann Committee—
to review the entire subject with special reference to the feeding
of antibiotics to livestock.

It was thought that if such a transfer of multiple drug resist-
ance should occur among livestock, with otherwise drug-sensitive
strains of disease organisms which also could infect humans, then
there was the possibility that a serious epidemic of disease could
develop among the public that might not be controlled with any
available drug or antibiotic. This was admittedly a horrifying
prospect, if it were reasonably likely to occur.

That such a nightmare is unlikely is attested to by the fact
that over the past 24 years in the United States and Canada
literally tens of billions of head of livestock were fed a wide array
of antibiotic and other drugs over a broad range of doses—without
a single medically annotated incident of such a multiple-
drug-resistant disease moving from any kind of livestock into the
human population and creating an uncontrollable epidemic.

The incident which triggered the concern in England did not
in fact concern the everyday feeding of antibiotics to livestock.
For the alleged original source of the resistant disease (Salmonella
typhimurium) came from a group of clearly mishandled new
born calves not fed colostrum before shipping. The calves had
received a "shotgun" injection of several drugs.

The disease became rampant among the calves, killing half of
them, and allegedly reaching a children’s hospital, where six infant
fatalities occurred before the outbreak was brought under con-
trol.

Actually, of course, the drug of choice for treatment of this
particular infection in humans (Salmonella) is not one of the
tetracycline antibiotics. They are largely ineffective against this
organism at normal feeding levels, and therefore would not have
exerted any significant selective effect. The best antibiotic to have employed would have been chloramphenicol, which is not fed to farm livestock.

Succeeding laboratory investigations did, however, reveal that the particular strain of the intestinal organism involved (E. coli phage type 29) did possess the inherent resistance transfer factor (RTF) and was indeed resistant to several commonly fed antibiotics. In lab cultures it could readily transfer to the otherwise antibiotic-sensitive organism (Salmonella), rendering it also drug resistant.

The interpretation then was made that such resistant organisms in humans are derived from antibiotic-fed livestock. And the final recommendations of the Swann Report were that all such antibiotic feeding of livestock should be suspended in the United Kingdom except under the direct supervision of a veterinarian. After public and Parliamentary debate which extended for nearly two years, the ordinance was implemented.

Although the use of antibiotics in animal feeds in the United Kingdom is now more closely controlled than previously, they continue to be fed under professional supervision, and no further serious human disease problems have been reported.

In the United States the feeding of antibiotics is presently under review. But as no hazards to public health have been demonstrated, the practice is not as yet restricted, beyond the specifications of use required in the Federal registration of every antibiotic and drug.

In the meantime further research has uncovered several interesting and reassuring facts:

- Transfer of drug resistance between differing species of bacteria occurs much more readily and frequently under artificial laboratory culture conditions than it does in the intestines of living animals. Whether the rapid transfer observed in the laboratory is largely an artificial effect, or whether the competition within the living intestines tends to prevent the transfer, is not yet clearly defined. However, it has been shown to occur in the living intestines, although rather infrequently

- It has also been shown that cultures of bacteria into which resistance has become transferred can quite readily lose it again. Perhaps this also occurs even more rapidly within the living intestine. Certainly the evidence reveals that cultures with transferred resistance grow less vigorously after the transfer than they did
before. This would render them less capable of survival as they become "overgrown"

- Cultures into which drug resistance has been transferred are often, though not invariably, less capable of inducing disease in the host than were the previous drug-susceptible cultures. They often differ in visible shape and appearance and generally show a considerably reduced rate of growth.

The potential evolution of pests of any kind that are resistant to control procedures—whether bacteria, fungi, internal parasites or insects—is of course a constant concern to all producers of crops and livestock. On balance, however, the threat falls far short of the very certain losses that invariably occur when no controls at all are employed against such pests. The only question of merit is the one of the risk : benefit ratio to man.

In the use of antibiotics in agriculture, primarily for livestock production, the risk : benefit ratio weighs so heavily in favor of benefit that there should really be little dispute.

It has been estimated that withdrawal of the use of antibiotics from livestock production would promptly raise the cost of meat and animal products by at least $1 billion a year at the consumer level.

Such an inordinate and really quite unnecessary increase in food costs would incite considerable public reaction both in the United States and in many foreign countries.

On the other hand, the proposed risks from the continued use of antibiotics in agriculture are in fact essentially unsupported by experimental evidence, public health considerations, or practical field experience extending, by now, for over 20 years.