cluding all contributions to it, as a phenomenon. Phenomena in scientific communication are not common: a full appreciation of their significance requires more analysis than results from a simple listing of their outward characteristics. But a few observations might be made in conclusion.

Most United States scientists probably feel that, as a nation, we are and should be world leaders in science, even though this feeling is neither nurtured nor expressed in a spirit of violent competition. If this assumption is allowed, the point which seems to remain is that the United States will not retain its position casually. Our scientists expect to maintain an awareness of the scientific achievements and failures of the other nations of the world. But we must especially become more aware of the advances of Soviet science, both qualitatively and quantitatively. The evidence points toward this last conclusion, regardless of whether one is concerned with the production of ideas or things, increase in man's knowledge of himself and his environment, conflict between idealisms, or simply the national security.

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Penalty of Isolationism

Selman A. Waksman

The identicalness of two antibiotic preparations, one isolated in 1946 and designated as "grisein" (*1*) and the other isolated 5 years later and designated as "albomycin" (*2*), leads once more to a sad reflection of the penalty that must be paid for scientific isolationism, which may even be colored by scientific nationalism.

If ever isolationism has been dangerous in any field of science, if ever rapid development in such a field has required close international collaboration among different scientific groups, it has been particularly true of the study of antibiotics. The study of the formation, isolation, chemical identity, and biological activities of these microbial products requires rather specialized procedures in biology and biochemistry. Our knowledge of antibiotics and their extensive applications is of only very recent origin. It involves a knowledge of the antibiotic-producing organisms, which may vary greatly in nature, of the chemical substances produced by these organisms, of the antimicrobial activities of these substances, their pharmacological properties, and their practical potentialities as therapeutic agents.

One of the most striking illustrations of the need for close collaboration in this field was recently presented by the isolation in four different laboratories in the United States and in Western Europe of preparations which, on careful comparison, proved to represent the same chemical and biological entity. This could be established, not only by a comparison of the physical and chemical properties of the preparations, but even more simply by the use of organisms of known sensitivity to different antibiotics. Developments in the case of grisein and albomycin would seem to provide an equally striking illustration.

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Isolation of Grisein

Following the isolation in our laboratory, from cultures of actinomycetes, of actinomycin in 1940, streptothricin in 1942, and streptomycin in 1943, the search for organisms capable of producing antibiotics that were active upon bacteria resistant to streptomycin was continued. This search resulted in the isolation in 1946, from the Huleh peat of Israel, of a strain of *Streptomyces griseus* that produced an antibiotic different from streptomycin. It was designated *grisein.* This antibiotic inhibited in very high dilutions the growth of certain Gram-positive bacteria, such as *Micrococcus pyogenes* var. *aureus* (*Staphylococcus aureus*) and *Bacillus subtilis,* and of Gram-negative bacteria, such as *Escherichia coli* and *Serratia marcescens.* The activity of the antibiotic produced by this culture was much greater against staphylococci than against *Escherichia coli.* Unlike streptomycin, it had no activity against *Bacillus mycoides, Proteus vulgaris,* and *Salmonella typhosa,* and only limited activity against mycobacteria. Sensitive bacteria rapidly developed resistance to grisein, so much so

that the broth-dilution method could not be used for measuring its concentration.

Grisein was adsorbed on charcoal, removed with neutral alcohol, and precipitated with methanol. It was insoluble in ether, chloroform, absolute acetone, absolute ethanol, and benzene. It was water-soluble and heat-stable. It possessed but little toxicity to experimental animals. It was active *in vivo,* protecting experimental animals against infections with *Micrococcus pyogenes* var. *aureus* and *Salmonella schottmülleri.*

The addition of iron salts to the medium had a highly favorable effect on the yield and activity of grisein. This was true particularly for synthetic media, in which a direct parallelism was obtained between the concentration of iron and the production of grisein (*3*). However, addition of an excess of iron to the antibiotic preparation reduced its activity. There were marked differences in the chemical composition and biological behavior of grisein and streptomycin, as was evidenced by the sensitivity of streptomycin to sulfhydryl and carbonyl groups and by the absence of such sensitivity in grisein, and there were also differences in the antibiotic spectra; there was no cross resistance between the two antibiotics. Strains of *Streptomyces griseus* producing griseinlike antibiotics were soon isolated in our laboratory from the intestinal contents of a heifer (*4*) and from a Japanese soil (*5*).

Upon further study, it was decided that the narrow antibiotic spectrum of grisein and the readiness with which bacteria developed resistance to it hardly justified the use of this product in clinical medicine.

Kuehl and his collaborators (*6*) proceeded with the isolation of chemically pure grisein. They succeeded in obtaining preparations of a very high potency and giving an activity of 300 million *Escherichia coli* units per gram. The pure grisein was a red amorphous powder soluble in water and phenol. The chemical formula of $C_{40}H_{61}N_{10}O_{20}SFe$ was assigned to it. Hydrolysis of the grisein preparations gave a large number of amino acids, one of which was identified as glutamic. The iron in the molecule was found to be in a ferric state. It could be removed from the complex, giving colorless and partly inactivated preparations. When a small quantity of iron was again added to the preparation, the color and the high level of antibiotic potency were restored. An excess of iron inactivated grisein.

Isolation of Albomycin

In 1951, Gause and Brazhnikova (*7*) reported the isolation from a culture of *Streptomyces,* referred to as *Actinomyces subtropicus* (*8*), of a new antibiotic, which was named *albomycin.* This antibiotic was found, when tested by the agar-diffusion method, to inhibit the growth of various Gram-positive cocci and certain Gram-negative bacteria, including those resistant to other antibiotics. Pure preparations of albomycin were active against staphylococci in a dilution of 1 to 700 million (*9*). Like grisein, it had no activity against *Bacillus mycoides* and *Mycobacterium tuberculosis.* It was practically nontoxic to animals. Pure albomycin was an amorphous red powder, soluble in water, and insoluble in organic solvents. Its characteristic property was a high content of iron (4.16 percent). When the iron was removed from the albomycin molecule, the orange color of the preparation disappeared and its antibacterial activity was greatly reduced. When the iron was again added to the antibiotic preparation, the color and activity were restored. Albomycin represented a cyclic polypeptide, which gave, on hydrolysis, various amino acids, one of which was glutamic. The adsorption spectrum reported for albomycin corresponded exactly to that of purified grisein—namely, maximum distinguishing peaks at 265 and 420 millimicrons. A molecular weight of about 1300 was assigned to albomycin. It was active only in the presence of oxygen. Increasing additions of iron decreased the activity of the antibiotic (*10*).

Grisein Reexamined

A comparison of the antimicrobial, physical, and chemical properties of albomycin with those of grisein leads one to the inevitable conclusion that the two are closely related if not identical. No comparison could be made of the cultures that produced the two preparations, for the Soviet culture was not available for study. It is rather surprising that in none of the Soviet papers cited in connection with the work on albomycin was there any comparison between albomycin and grisein, although in one paper there is a brief comment that grisein is the only other antibiotic containing iron, but that the antibiotics differ. The only apparent evidence submitted to support this statement is found in a reference (*7*) to the fact that grisein is not active against *Aerobacter aerogenes,* while albomycin is active against this organism. Obviously, the strains of the test organism could have been different, since no attempt known to me was actually made to compare the two antibiotic preparations.

In a comparative study of some recently isolated antibiotics, Garrod and Waterworth concluded (*11*) that albomycin was the least promising. They emphasized also that the broth could not be used for testing purposes, since this antibiotic failed to inhibit the growth of *Micrococcus pyogenes* var. *aureus,* although it did so in agar media. Among the Gram-negative bacteria, *Escherichia coli* was sensitive to albomycin, whereas *Proteus mirabilis, Salmonella typhosa,* and *Pseudomonas aeruginosa* were highly resistant. They also noted, among sensitive organisms, the rapid development of resistance to albomycin. All these properties are characteristic of grisein.

Elsewhere in this journal, Stapley and Ormond (*12*) present experimental evidence "that albomycin and grisein are chemically very similar and identical with respect to antimicrobial activity." Just as was reported (*1*) for grisein, albomycin is highly active against *Micrococcus pyogenes* var. *aureus* and *Salmonella schottmülleri,* and it shows little activity against *Salmonella typhosa* and *Proteus vulgaris.* Biological identity of the two preparations is further substantiated by their activity against sensitive strains of *Escherichia coli* and their lack of activity upon resistant strains of this organism.

Summary

Research on new antibiotics is engaged in at present throughout the world with such intensity that one must be able to compare cultures of organisms producing such antibiotics, as well as the isolated substances themselves, if one is to avoid needless duplication and great confusion. As long as no international center exists where such comparisons can be made, only close collaboration among scientific laboratories can make possible these essential comparisons. The repetitions and the frequently unjustified creation of "new species" of antibiotic-producing organisms and of "new antibiotics" can be avoided only by close collaboration among the scientific workers throughout the world. The creation of an International Antibiotics Board is also highly essential at the present time.

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Similarity of Albomycin and Grisein

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In the course of an investigation into the nature of albomycin, an antibiotic described by Gause (*1*) as a product of *Actinomyces subtropicus*, considerable data have been obtained indicating similarity of this product to grisein, which has been described by Reynolds, Schatz, and Waksman (*2*) as a product of *Streptomyces griseus*. We have also obtained information on the existence of several components in partially purified grisein which have not been described previously.

Information on the chemical constitution of grisein and albomycin published by Kuehl, Bishop, Chaiet, and Folkers (*3*) and Gause (*1*), respectively, suggests possible similarity, since both antibiotics are described as red-colored, amino-acid containing, iron complexes. Both substances are very active on a weight basis against sensitive bacteria.

Materials and Methods

We have had available ampules of albomycin obtained from international sources and also a preparation of albomycin obtained directly from G. F. Gause through S. A. Waksman. The potency of the albomycin employed in our studies was 91,000 units per milligram. Comparison was made with two partially purified concentrates of grisein prepared at Merck and Company, Inc., that were active at 41,000 and 22,000 units per milligram, and with a crude preparation of grisein prepared in the laboratory of S. A. Waksman in 1948, which proved to be active at 312 units per milligram in a recent assay. All assays were performed by the agar diffusion method with *Escherichia coli* as the test culture and a standard based on an assigned value of 300,000 units per milligram for the pure grisein of Kuehl *et al.* (*3*).

Paper-strip chromatograms were developed on Whatman No. 1 filter paper. Bioautographs were obtained by placing air-dried paper strips on the surface of large baking dishes of nutrient agar seeded with *Escherichia coli* W followed by incubation at 25°C for 18 hours. Ascending paper chromatograms were developed at room temperature until the solvent front had moved 25 to 30 centimeters. Descending paper chromatograms were run so that the fastest moving component had traveled approximately 24 centimeters in 52 hours when they were developed at 28°C with a solvent mixture of butyl alcohol (4 parts), acetic acid (1 part), and water (5 parts). The strips were developed with the solvent phase after a 3-hour equilibration with an atmosphere saturated with the water phase.

Column partition chromatography was accomplished by pouring a solution of 1.1 grams of grisein (22,000 units per milligram) in 40 milliliters of upper phase from an *n*-butyl alcohol (4 parts), acetic acid (1 part), and water system (5 parts) over 800 grams of pulverized paper wet with lower phase. The column was developed with upper phase. Starting just before the first yellow eluate came off the column, 25-milliliter aliquots were collected, absorption at 4250 A was determined, and the reading was plotted. The peak fractions were combined, concentrated in a vacuum, and lyophilized. Repartition of 134 milligrams of a combined fraction (Fig. 1, tubes 71 to 150) with 60,000 units per milligram containing mainly component C was carried out in the same fashion as the original column partition, using 300 grams of pulverized paper. Eluate aliquots of 9 milliliters each were taken by a fraction collector, and the ultraviolet absorption at 4250 A was measured.

Data from the column partition were compared with a 39-plate countercurrent distribution of grisein (41,000 units per milligram) employing 2*M* phosphate buffer at *p*H 6.7 and 10 grams of solid phenol diluted to 100 milliliters with chloroform. The countercurrent fraction where $K = 0.26$ corresponded to the fraction from which pure grisein was originally obtained by Kuehl *et al.* (*3*).

Results and Discussion

In our tests of grisein and albomycin, we noted that the inhibition zones produced on disk or cup-plate assays were very similar, especially with regard to the rapid appearance of resistant colonies within the inhibition zone. The capacity of grisein to permit exceptionally rapid development of resistance and the characteristic hazy appearance of inhibition zones produced as a result of rapid development of resistance have not been

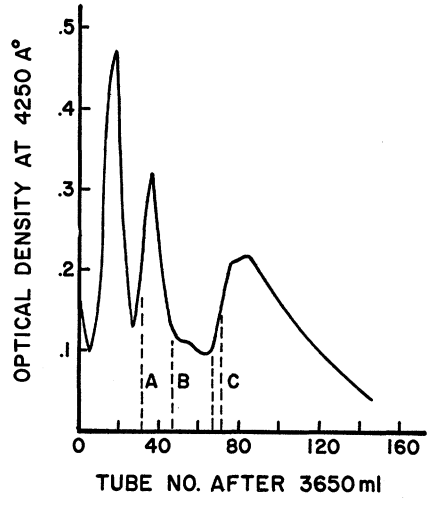

Fig. 1. Column: partition chromatography of grisein. The curve shows the ultraviolet absorption at 4250 A of 25-milliliter aliquots eluted from a cellulose column that was charged with grisein (22,000 units per milligram).

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