CHEMISTRY-MEDICINE

Antibiotic Synthesized

Chloromycetin is the first antibiotic to be synthesized on a practical basis. This drug has been effective in curing viruses and rickettsial diseases.

See Front Cover

➤ FOR the first time in history a disease-curing mold chemical, or antibiotic drug, similar to penicillin, has been synthesized on a practical basis.

The drug is chloromycetin which has been curing scrub typhus and other kinds of typhus fever, typhoid fever, Rocky mountain spotted fever, undulant fever, virus pneumonia, whooping cough, Friedlander's pneumonia and some other germ infections.

The synthesis was achieved by pretty, 28-year-old Dr. Mildred C. Rebstock, research chemist at Parke, Davis and Company in Detroit where production of the drug from the mold has been going on for about two years.

First news of its synthetic production reached scientists through a report by Dr. Joseph E. Smadel of the Army Medical Department to the Society for Experimental Biology and Medicine (Proceedings, *Feb.*).

Details of the synthesis were reported by Dr. Rebstock and Dr. Harry M. Crooks, Jr. and John Controulis of Parke, Davis at the American Chemical Society meeting in San Francisco this week (Mar. 29).

Tests on embryonated eggs, mice and two human patients with scrub typhus fever showed that the synthetic chloromycetin is as effective as the mold-produced one, Dr. Smadel reported. In these tests it was tried against scrub, epidemic and murine typhus fevers, spotted fever, psittacosis (parrot fever), rickettsialpox and the lymphogranuloma virus.

Working with him in these tests were Drs. Elizabeth B. Jackson, Herbert L. Ley, Jr., and Raymond Lewthwaite of the Army Medical Department and Major C. J. Williams, RAMC, of the Military Hospital, Kuala Lumpur, Malaya.

Penicillin, first of the antibiotic drugs, was synthesized after years of intensive efforts by teams of scientists in the United States and in England. But this synthesis was a laboratory feat not suitable for production of usable quantities of the drug.

The chloromycetin synthesis is on a practical large-scale production basis. Parke, Davis and Company are now producing the drug by the fermentation process from the mold and by the synthetic process. The synthetic chloromycetin has been named Chloramphenicol.

Both kinds of chloromycetin are now on the market. Originally, the supply was so small that it could only be used for clinical trials by a limited number of physicians. But with two kinds of production going, the manufacturers have been able to release it through regular channels, though this has been done so recently that drug stores in some communities may not yet have supplies.

With two ways of making the drug, it is hoped that the price will soon drop. At present, the best price, to institutions such as hospitals, is somewhat over $2 per gram. At retail drug stores it may sell for considerably more. Doctors now use from eight or nine to 20 grams for each patient treated. With more experience they may find that less of the drug is needed. Right now, they give maximum amounts to avoid relapses or failures to get the patient well.

The mold that makes chloromycetin has been christened *Streptomyces venezuelae*. The first word of the name shows the class of molds to which it belongs, which incidentally is the same as that which produces streptomycin. The second word is in honor of the country, Venezuela. It was in a sample of soil from this South American nation that Dr. Paul R. Burkholder of Yale University discovered chloromycetin. Dr. Burkholder, working under an arrangement with Parke, Davis and Company, had been testing hundreds of soil samples from all over the world in a search for new antibiotic drugs.

First use of the drug was, appropriately enough, in Venezuela's sister country, Bolivia. A typhus epidemic had broken out and Parke, Davis was asked by the Bolivian health officials if they had any drug that would help. They got together all the chloromycetin they had, amounting to a few grams, and Dr. E. H. Payne of the company flew down with it. The first 40 patients treated all got well, whereas 20 of the 50 previous typhus victims had died.

Because scrub typhus, or tsutsugamushi disease, had been a worry to the Army during the Pacific phases of the war, next trials of chloromycetin were made by Dr. Smadel in Kuala Lumpur. There it proved its effectiveness against this disease and also against typhoid fever.

Hope that chloromycetin might become a cure for the common cold has been raised by its effectiveness in some virus diseases. A few physicians have tried it and reported good results, but there have been no scientifically controlled trials of it in colds as yet. The manufacturers doubt whether it will prove effective in either colds or that other virus-caused plague, for which a remedy is still badly needed, infantile paralysis.

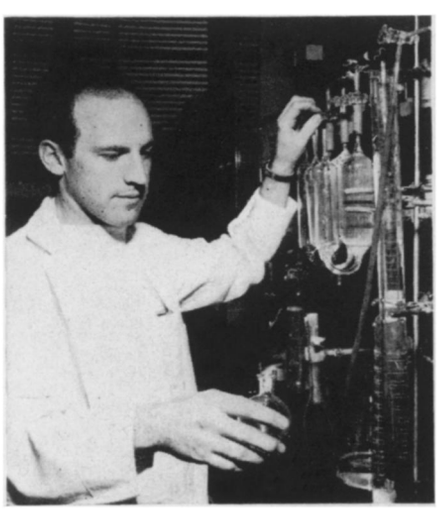
For diseases in which the drug is effective, the response comes, as one doctor puts it, "with monotonous uniformity," within two to three days. This response is so uniform that doctors now feel they can test the drug's effect by it in diseases for which it has not yet been used. If the patient is not getting well by the third day, the drug is not going to be effective in his particular disease.

When the mold-produced drug had shown its value as a cure for scrub typhus, Dr. Crooks was asked to coordinate the project of finding a way to produce synthetic chloromycetin on a practical basis.

First he, with Dr. Rebstock, John Controulis and Dr. Quentin R. Bartz, worked out the chemical structure of the chloromycetin molecule. Then Mr. Controulis, in a remarkably short period of time, developed a synthetic method of production.

Unfortunately, the arrangement of the atoms in his synthesized product was wrong and the chemical was not active against disease germs. The work was then turned over to Dr. Rebstock, who developed the method for practical synthesis of the active drug. She is a graduate of North Central College, Illinois, received her Ph.D. in chemistry at the University of Illinois, and has been on the Parke, Davis research staff four years. Dr. Rebstock is pictured on the front cover of this week's SCIENCE NEWS LETTER showing samples of her chloromycetin to Dr. Payne, first man to use the drug on human patients.

Chloromycetin, unlike penicillin and strep-



John Controulis, Parke-Davis chemist, is shown with the apparatus used in the synthesis of chloromycetin.

tomycin, is effective when given by mouth, and its toxicity is of a very low order. So far, no reports of any serious side-effects have been made.

In the process of making the synthetic drug, several surprising facts about it were discovered. For the first time a natural compound was found containing a nitrobenzene grouping. This chemical grouping has always been thought harmful to animal life, but in chloromycetin it is harmless. The chemists also found that the drug is a derivative of dichloroacetic acid, another compound never before found in a natural product. Its chief medical use in the past was for the removal of warts. Thus by two counts the mold-drug should have been toxic but is not.

Chemists now are working on preparation of closely related structures which may have even wider usefulness in medicine than chloromycetin itself. Two other Parke, Davis chemists, Dr. Loren M. Long and Harvey Troutman, have already developed a second feasible method of making chloromycetin commercially on a large scale.

Chemically, chloromycetin, or chloramphenicol, is D-threo-1-paranitrophenyl-2-dichloroacetamide-1,3-propanediol.

Science News Letter, April 2, 1949

CHEMISTRY

Acetylene Used Safely

➤ CHEMICALS from acetylene are to be made in Grasselli, N. J., under high pressures and temperatures with safety in a plant just opened by General Aniline and Film Corporation of New York. It is the first establishment of its kind in the United States.

Acetylene, long known to chemists for its wide versatility but little used because of its explosiveness under pressure, can now be exploited with safety as a result of new techniques, Dr. Carl Marvel said at the dedication exercises. With this development a whole new field of organic synthesis is opened up which should prove of intense interest in the manufacture of resins and adhesives, pharmaceuticals, paper, rubber and textiles.

The technique to be used there is based on processes developed in Germany during the war. Briefly it consists of two methods, one involving the dilution of acetylene with an inert gas, and the other one in which acetylene is reacted in what is essentially small-bore equipment providing a minimum space for gases to collect.

EXPLOIT EXPLOSIVE — Huge tanks provide storage capacity for vinyl ethers, alkynols and other acetylene derivatives in this first U. S. high pressure acetylene plant.

With a shortage of hydrocarbons, the Germans during the war were compelled to find new raw materials for essential wartime chemicals especially for the production of synthetic rubber, pharmaceuticals and synthetic fibers. Derivatives of high-pressure acetylene answered these needs and played a vital role in Germany's ability to carry on for nearly six years.

At the opening meeting, Dr. Hans Beller of General Aniline said that the high reactivity of acetylene under pressure makes it perhaps the most versatile tool available to the organic chemist, and that for this reason it is impossible to predict with much hope of accuracy the full extent to which acetylene derivatives may contribute to future economy.

Acetylene is a well known gas easily made by adding water to calcium carbide. Uncontrolled, it is an explosive. It burns with an intensively hot flame, which accounts for its use in the well-known oxygen-acetylene torch used in welding or cutting metals. It is already the starting point for the synthesis of a large number of organic compounds. It can be made in large quantities, the basic materials being limestone and coke, used to make the calcium carbide.

Science News Letter, April 2, 1949

AGRICULTURE

American Know-How to Help Other Countries Grow Food

➤ THE United States and Canada, which have been heavy exporters of food during the world's post-war emergency, are now beginning to export improved seed and agricultural know-how that will enable countries where recovery has started to increase their own supplies. How this is happening was related in a talk by Gove Hambidge, adviser to the Director-General of the Food and Agriculture Organization of the United Nations. Mr. Hambidge spoke as guest of Watson Davis, director of Science Service, in the Adventures of Science series, heard over the Columbia network.

Despite the great losses of life during the war the population of the world is increasing rapidly, the speaker stated. Every day some 55,000 new mouths to feed are added to the total of the day before. At the same time, the amount of food per person now being produced is below the pre-war level. And emergency exports from Noth America cannot go on indefinitely.

The problem is aggravated, Mr. Hambidge pointed out, by the fact that the very countries where the population is greatest and increasing most rapidly are the ones where production methods have lagged most in their development. It is imperative, he declared, not only to help them grow more food but to find ways to get some of their surplus population off the land and into industry, so that the land may be more efficiently farmed by fewer people using better methods.

"For a widespread development job," he said, "the main needs are technical skill, equipment, and funds. Some of the money will have to come from public international funds, especially to get developments started. Some will be drawn from national treasuries, both within and outside of the countries where extensive developments are taking place. Much may come from the investment of private capital.

"The equipment necessary for expanded production—for example, equipment for irrigation and for transportation—will have to come at the start from the highly developed countries. So will most of the trained technical workers. Gradually, however, these resources of materials and skills will increase in the countries undergoing development."

Science News Letter, April 2, 1949

AERONAUTICS

British Twin-Jet Fighter Has Great Climbing Speed

➤ A BRITISH twin-jet fighting plane recently climbed seven-and-one-half miles in seven-and-one-half minutes. It is said to be the fastest climb on record with the exception of that made by the American Air Force XS-1, a rocket plane, and perhaps by other rocket-powered aircraft.

The plane that made this remarkable climbing speed was an experimental Beryl-Meteor twin-jet fighter. It climbed two miles in the first minute, and took only three minutes to reach a five-mile altitude. Experts in London believe that with the use of newer and still more powerful jet engines, British fighters will be able to equal the climb-rate of the rocket plane.

Science News Letter, April 2, 1949