sible to employ chlorophyll to fight bacteria? Even the best antiseptics usually have one disadvantage in that, if they are strong enough to kill the causes of the disease, they often disturb the function of the surrounding tissue at the same time. Might chlorophyll enable the body to fight the invading bacteria and yet spare the tissue?

Laboratory experiments have shown that, in itself, chlorophyll does not have the power to kill off bacteria. But when it is in contact with live tissue it seems to strengthen the cells' power of resistance and to hamper the growth of bacteria. Its specific ability of breaking down carbon dioxide and releasing the oxygen spells doom for the bacteria, which can only live in suppurating wounds beyond the reach of air. Even in generous doses chlorophyll has shown no irritating effect. The department for experimental pathology at Temple is now preparing various ointments containing chlorophyll for all kinds of infections and is experimenting with them. Incidentally, ointments containing chlorophyll, usually in addition to sulfonamides, have already been marketed in China.

Last year, a dozen well-known doctors published their experiences with chlorophyll in the *American Journal of Surgery*. All in all, some 1,200 cases, from deep-seated infections to superficial skin injuries, had been treated by these men, and in case after case the report ended: case cured. Patients arrived with a ruptured appendix and incipient peritonitis; after the necessary operation, a chlorophyll solution was successfully applied to the deep wound by means of a tube. In other cases a compress with chlorophyll or an ointment containing chlorophyll was applied. Serious bone diseases, inflammation of the brain, and many cases of mouth infections, *angina vincenti*, and *pyorrhea alveolaris* have been cured.

For quite a number of years, chlorophyll preparations for injection have been marketed by reputable firms for the treatment of tuberculosis and arteriosclerosis. The American specialists Robert Ridpaths and T. Carroll Davis have had excellent results in the treatment of 1,000 cases of infections of the respiratory organs. They reported that they had not seen a single case treated with chlorophyll where the patient had not been either completely cured or at least shown considerable improvement. Chlorophyll tampons inserted in the nose during colds have been outstandingly successful in giving instant relief. Patients with a cold in the head or the nose were greatly relieved within twenty-four hours.

How does chlorophyll destroy bacteria or hamper their growth? Beyond the facts that it strengthens the cell walls, hampers the growth of the bacteria, and gives the body a chance to mobilize its own defenses, doctors know very little. Perhaps there is something in the theory that the effect produced by chlorophyll is produced by its hampering influence on the vitamin metabolism of the bacteria, which latter are—like humans and animals—dependent on the presence of certain substances of a vitamin character.

PENICILLIN—MEDICINE FROM MOLD

By HANNS WIRTZ

During the last few months, various sensational reports have appeared in the press about a new drug called penicillin which is supposed to possess miraculous healing properties. "Time," in its issue of March 15, 1944, went so far as to say: "Penicillin will save more lives than war can spend," and even Churchill mentioned the new drug in one of his speeches.

We have just received detailed material on penicillin from Europe, and Dr. Hanns Wirtz of Shanghai, who obtained his degree in pharmaceutics at the University of Bonn, Germany, tells our readers about the nature and significance of the new medicament in the following article.—K.M.

WHEN Robert Koch proved more than sixty years ago that a certain group of diseases, now known under the collective name of "infectious diseases," has its cause in the activity of numerous kinds of tiny parasites such as bacteria, protozoa, or fungi, he laid the foundation for effective countermeasures. Once an enemy is recognized, it is possible to lay bare his weak points and to construct the necessary defensive weapons. The same applies to the infectious diseases. Starting out from Koch's

discovery, several methods for their prevention or cure were developed. At first the greatest success was achieved by the injection of the blood serum from animals that have been inoculated with the respective bacteria or their toxins. Such serums, when introduced into the human body, provide it with the necessary power to resist and combat an infection by virtue of the antibodies it contains. In addition to this serum therapy, chemotherapy was evolved, i.e., the treatment of the disease by chemical reagents that have a toxic effect upon the microorganism causing the disease, without seriously harming the patient.

The success of this latter method, the wide employment of which began with Germany's Gerhard Domagk's publication on his experiments with sulfa drugs in 1935, was so overwhelming that it appeared at first as if this was the only promising method of combating such infectious diseases as pneumonia, typhoid, angina, scarlet fever, or gonorrhea. Hence the experts of the whole world turned their attention to testing and improving the sulfa drugs, with the result that another promising discovery in this field lay fallow for many years.

In 1928 Dr. Alexander Fleming, Professor of Bacteriology at St. Mary's Hospital Medical School, University of London, was studying the growth and properties of staphylococci, a genus of cocci bacteria most commonly found in boils, abscesses, carbuncles and similar suppurative processes. One day he observed that part of the medium in which he was culturing these staphylococci had been invaded by mold. A few days later, Dr. Fleming noticed that the mold had cleared a wide, bacteriafree area between itself and the staphylococci—perhaps had killed them. Realizing the importance of this phenomenon, he began to devote his attention to it. First he identified that particular mold as *Penicillium notatum*, a close relative to the ordinary mold, *Penicillium glaucum*, that annoys us by its appearance on stale bread, shoes, imperfectly sealed preserves, etc. Dr. Fleming then grew the mold on a liquid medium in glass containers. The mold secreted a substance into the medium which was capable of preventing the growth of disease-producing microorganisms. Dr. Fleming named this by-product penicillin.

Although several similar antibiotics—i.e., antibodies produced by bacteria to stem the growth of their rivals—were known, none had so far been employed successfully in medicine. The reasons for this were their comparative toxicity and the difficulty of producing them.

Fleming therefore examined his penicillin especially for its toxic effect on the animal organism and found that the medium containing penicillin was no more poisonous to animals than the pure medium. Above all, penicillin did not harm the white blood corpuscles, the human organism's chief troops of defense against harmful germs.

After the therapeutic effect of penicillin had been proved by excellent results in the treatment of infected wounds with a liquid containing penicillin, the question of producing it was studied. Although it became possible in 1932 to raise the mold in a synthetic medium, the penicillin itself could not be extracted in a concentrated, stable form without losing its effectiveness. Numerous attempts to overcome this difficulty were unsuccessful. And when in 1935 the sulfa drugs, which combine normal conditions of manufacture with their great effectiveness and comparatively low toxicity, commenced their triumphal march against the infectious diseases, Dr. Fleming and other researchers on penicillin believed that the latter would hardly attain any practical significance as an antiseptic beside the sulfonamides.

With the increasing employment of the sulfonamides, however, it became apparent that, beside the various bacteria they succeed in laying low, there are some germs which are insufficiently or not at all affected. It also turned out that the therapeutic result depends to a large extent on whether the drug can reach the focus of infection in an effective concentration. In cases where the infection has advanced to a stage at which necrosis, phlegmon, or thrombosis has set in, the chances of a cure have proved to be limited.

Hence medical science began to seek for means of closing these gaps. According to the Shanghai *Times Week* of August 9, 1944, Japanese research workers have been experimenting with penicillin for ten years. In England Dr. H. W. Florey and Dr. E. B. Chain of Oxford's Sir William Dunn School of Pathology resumed the interrupted work with penicillin. With the aid of a large research team, they succeeded in developing a method by which penicillin could be extracted from the culture medium and rid—at least partial-

ly—of impurities without destroying its efficacy. Now it became possible to study the bacteriological and pharmacological characteristics of penicillin by means of experiments on animals. The following important facts were established:

(1) Absence of any toxic effects on mice or other animals.

(2) White blood corpuscles and tissue cultures are not harmed by concentrations several hundred times greater than are necessary for preventing the growth of bacteria.

(3) The efficacy is affected neither by blood, pus, nor putrefaction of tissues.

(4) The efficacy is also scarcely affected by the number of bacteria present.

(5) Penicillin is absorbed when injected into muscle or blood stream.

(6) Penicillin is useless when given by mouth as it is destroyed by acid stomach juices.

(7) Penicillin disappears from the blood within two hours, being largely excreted in the urine; hence large doses must be given at short intervals for several days.

The examination of the efficacy of penicillin on the germs of the various infectious diseases showed that penicillin, too, is no panacea against all pathogenic germs. The following bacteria proved to be particularly sensitive to the drug: *Streptococcus pyogenes* (suppurating wounds, puerperal fever); *Staphylococcus aureus* (diseases of the bone, carbuncles); *Streptococcus pneumoniae* (pneumonia); *Corynebacterium diphtheriae* (diphtheria); *Clostridium welchii, septicum, oedematiens* (gas gangrene); *Neisseria gonorrhoeae* (gonorrhea); *Neisseria meningitidis* (meningitis, typhus). Less sensitive were, on the other hand, the germs causing typhoid fever. Wholly resistant were those of plague, cholera, dysentery, and tuberculosis.

Penicillin's effectiveness consists in that it prevents the dividing and multiplying of the bacteria affected by it. The drug is, in effect, as the technical term has it, a bacteriostatic, while most antiseptics as, for example, carbolic acid, kill the bacteria directly.

Although the characteristics of penicillin were now known and the experiments on animals had provided good results, the drug was still far from being introduced into general medical practice. Again it was the sensitiveness of this organic substance which, in contrast to the sulfa drugs, placed great obstacles in the way of large-scale manufacture. It took months of work on the part of Dr. Florey's entire team to produce enough penicillin to treat one or two patients. Moreover, the first man treated showed violent by-effects in the form of fits of shivering and rising temperature, which were, however, traced to impurities which it was later possible to remove. Researchers successfully went to work to discover technical methods of production with a sufficient yield, so that today it has become possible to provide pure, concentrated penicillin preparations on a comparatively large and increasing scale. But it is doubtful whether it will ever be possible to cover all requirements by the culture method, as it is very difficult to protect the mold from bacteria in the air whose enzymes tend to destroy it. This problem will hence only be fully solved by the chemical synthesis of penicillin which, although probably possible, has so far not yet been effected. Before penicillin can be synthesized, its exact chemical composition must be known. However, the difficulties involved in obtaining the absolutely pure secretion of *Penicillium notatum* (there are at least 100,000 molds and fungi, and there are always spores of some of these molds in the air) have resulted in several formulas for the chemical composition of penicillin having been advanced so far. Some scientists regard it as a peptide of the formula $C_{24}H_{32}N_2O_{12}$; others claim it to be a hydroaromatic compound $C_{24}H_{34}O_{10}N^2$ or $C_{14}H_{19}O_6N$ or $C_{24}H_{36}O_{11}N$; and finally there is one group of scientists who maintain that penicillin is a nitrogenfree compound.

Nor is it possible to determine the weight of the penicillin contained in a given solution without an exact knowledge of the chemical composition, although the exact determination of the penicillin content of such a solution is essential to its therapeutical application. Hence the biological test method has been resorted to. That quantity of penicillin was determined which, dissolved in 50 cc of meat extract, was just able completely to arrest the growth of a specific culture of *Staphylococcus aureus*. This quantity was named an Oxford unit, or also a Florey or Heatley unit. In view of the rapid secretion of penicillin from the body, vast quantities of these units are needed. In the case of pneumococci infections, for instance, the amount of penicillin needed for a cure is around 100,000 Oxford units, while there

have been reports on the curing of serious streptococcus cases which mention the injection of 830,000 to 7,900,000 Oxford units.

According to the latest information, there are seven manufacturers in Great Britain and 21 in America (two Canadian, the rest US) now producing penicillin or soon to be in production. America expects about 200 billion units a month to be produced by the end of the year. The American factories will have a top capacity of nine pounds (almost 7 billion units) a day, compared with a total production last year of about 15 pounds. Prices now vary from US$2.85 to $10 for 100,000 units (last year's price: $20).

The small quantities produced until recently make it obvious that there are not nearly as many reports available on successful treatments as was the case some ten years ago when the sulfonamides were introduced. Nevertheless, there exists already enough material to permit the conclusion that, in cases where sufficient quantities of penicillin are obtainable, the drug can produce amazing results.

By far the greatest experience has been gained in the treating of war wounds with penicillin. The bacteriologist Florey and the surgeon Cairns of Oxford joined the British troops in North Africa and Italy for three months to make observations on the spot. After some initial failures, they obtained very favorable results. The danger of infection in the case of war wounds was practically eliminated. The best results were achieved by powdering the wounds with a mixture of penicillin and sulfonamide.

Extremely impressive results were attained with penicillin in the treatment of sulfonamide-resistant cases of gonorrhea which, with few exceptions, were cured in two days. Numerous cases of otherwise hopeless staphylococcus infections were also cured with penicillin, among them osteomyletitis (inflammation of the bone marrow), infections of the skin- and subcutaneous tissues (furuncles, etc.), and other infections.

In the case of pneumococcus and meningococcus infections, experience has proved favorable but not extensive, as here the excellence of the sulfonamides is undisputed, and there is no reason to employ penicillin for diseases in which simpler methods lead to the same result. The same applies to a large number of other infectious diseases, such as arthritis, infections of the urinary tract, infections of the nose, sinus, and ear, ulcers, cellulitis, infections of the hands, burns, etc. Many authors report on excellent results with penicillin in the treatment of these diseases; but at the moment these fields of indication are of no practical significance. For almost the entire present production goes to the armed forces for the treatment of all kinds of wounds, only a small surplus being released for the treatment of civilians. Naturally, this limited quantity is reserved mainly for such cases where other drugs have failed.

Whether penicillin will hold its own beside the proven medicaments used today, or whether it may even replace these, will only become apparent when the medical world can be supplied with unlimited quantities at competitive prices, which is not yet the case. It looks as if penicillin or similar by-products of other microorganisms, such as pyocyanase, tyrothricin, gramicidin, claviformin, patulin, spinulosin, citrinin, gliotoxin, aspergillin, flavicin, clavacin, and actinomycin, may be able to close the gaps left by the sulfonamide therapy. Various reports have already been published according to which most human and animal pathogenic germs can be arrested in their growth by one or the other antibiotic. This is also true of the particularly insensitive acid-resisting bacilli. Indeed, even the tuberculosis bacillus, which is otherwise practically impregnable, has been successfully attacked by preventing its growth, not by penicillin, but by actinomycin, an antibiotic analogous to penicillin but obtained from a different mold.

It would thus appear as if, with the aid of antibiotic and chemotherapeutic substances, practically all infectious diseases will be preventable or curable in future. It is also entirely within the realm of possibility — and this is Florey's opinion too — that an antibiotic will be obtained one day from one of the countless microorganisms which will prove to be the universal cure for all diseases caused by germs.

Perhaps a step in this direction has already been made in Japan, where Professer Dr. Masahiko Kuroya of the Tohoku Imperial University and his assistant Dr. Shikaji Kondo recently announced the discovery of a new type of penicillin with a fungus-growth-prevention power many times greater than that of Dr. Fleming's penicillin.