News and Comment

PENICILLIN

A little over a decade has passed since it was first observed that broth cultures of a certain strain of *Penicillium notatum* contained a substance, penicillin, which inhibited the growth of many gram positive organisms. During this period certain investigators in England, and in this country, have focused their studies on this substance with the purpose of determining its essential properties and its possible clinical field of usefulness. It may now be stated, with scientific caution, that these studies are beginning to bear fruit which is promising.

Among the early difficulties encountered in the study of penicillin were productibility and stability of the product. These problems have been largely solved.

Penicillium notatum is a mycelium or mould which grows readily in a variety of media, but for the production of penicillin the simplest and best medium is one containing principally brown sugar and small portions of various chemicals in distilled water. At the end of about seven or eight days, the penicillin can be extracted from the culture medium by organic solvents. Following the various extractions and filtering, the penicillin is extracted back into pyrogen-free water, saturated with ether or chloroform and the resultant extract is stable when stored in the refrigerator or dried by the lyophile process. The early problem of stability of the product has now been solved by the preparation of a sodium salt of penicillin which is extremely soluble, especially if obtained in sufficiently dry form and used for intravenous administration. A calcium salt of penicillin has been prepared for local application.

Experimental observations have established the bacteriostatic action of penicillin for a wide variety of organisms. Included among these are especially certain gram positive organisms, such as pneumococcus, hemolytic and nonhemolytic streptococcus, staphylococcus, and the clostridia group, and gram negative organisms, such as meningococcus and gonococcus. On the other hand, it has been found that certain organisms, such as the typhoid, paratyphoid, and dysenteric groups, the monilia group, and the *B. pyocyaneus*, are not susceptible to penicillin, and it

seems to be of little or no value in acute and subacute bacterial endocarditis. The extremely potent antibacterial activity of penicillin even in high dilutions combined with its relative innocuousness to tissue cells are its most attractive clinical properties. Its mechanism of action is not completely understood and may not be forthcoming until its constitution has been ascertained or its active principle isolated. On the basis of present knowledge it would seem that it does not belong to the sulfonamide group. In contrast to the sulfonamides which cause only a slowing up of the rate of growth of bacteria, penicillin produces an actual killing effect. Depending upon certain conditions, it may act either as a bacteriostatic or bacteriocidal agent. Experimentally, the number of organisms decrease at a constant rate until 99 percent of the organisms have been destroyed and the rate of killing varies with different organisms. Thus, pneumococci are more rapidly destroyed than hemolytic streptococci, which in turn are more rapidly destroyed than staphylococci. Moreover, no detectable amount of penicillin is destroyed or absorbed from solution by the organisms. It also appears to be effective when active multiplication occurs, and, in contrast to the sulfonamides, hydrolytic protein breakdown products or products of tissue autolysis (pus) do not antagonize its bacteriostatic power. *In vitro* studies have also revealed that even in high concentrations penicillin does not embarrass leukocyte activity. Experimental observations on the effect of penicillin on cerebral and other tissues have shown no pathologic lesions or functional disturbances. Apparently penicillin administered locally or intravenously even in strong solutions has proved innocuous to tissue cells.

Studies on absorption and excretion of penicillin reveal a number of interesting properties. It is readily absorbed after subcutaneous or intramuscular injection but is destroyed and is apparently of no value when given by mouth, by gastroduodenal intubation, or by rectum. None seems to enter the spinal fluid when administered intravenously or intramuscularly, and very little is absorbed from chronic infected cavities. It is rapidly excreted principally by the kidneys as shown by the fact that from 45 to 50 percent may be recovered in the urine within one hour after intravenous injection and all within two and one-half to three hours. Of particular interest is the fact that the material recovered from the urine continues to have a high antibacterial titer.

Penicillin may be administered by intravenous or by intramuscular injections or it may be used by local application. Because it is rapidly excreted, frequent injections are necessary. Dosage varies depending upon the condition but in the average septic case, the penicillin is prepared by dissolving the dry powder in normal saline solution so that a one cc. solution contains 1,000 units and 15,000 units are administered intravenously every three hours for several days following which the dosage is decreased according to the response of the patient. For intramuscular administration it is desirable to keep the total volume of individual injections small. Accordingly, when this route is used, penicillin is prepared in a concentration of 5,000 units per cubic centimeter of normal saline solution. It may also be employed locally in chronic intractable sinus and cavity infections.

Preliminary clinical observations reveal highly promising therapeutic potentialities. In a well-controlled study by a special committee of the National Research Council on a significantly large group of cases with sulfonamide-resistant infections, particularly notable results were obtained. Included in this series were intractable soft parts infections with draining sinuses, chronic osteomyelitis and infected compound fractures, old infected burns, empyema, and chronic gonorrhea resistant to other forms of therapy. While penicillin has not been used clinically in gas bacillus infections, experimentally the response has been especially favorable. Intensive and well-controlled clinical studies are now being conducted in specially equipped Army hospitals in order to ascertain more exactly the usefulness of this new drug, to determine its indications and contraindications, and to standardize the therapeutic procedures associated with its use. These considerations concerning the present status of penicillin as it applies to the Army have been presented in S.G.O. Circular Letter No. 125, 16 July 1943.

WHOLE BLOOD TRANSFUSIONS AT THE FRONT

The value of plasma transfusion in military practice is now well established, and dried human blood plasma has been made available to all medical installations in theaters of operations. It is realized, however, that whole blood transfusions will be required to supplement plasma, especially in cases of prolonged sepsis, in the later stages of burns, and in cases in which large amounts of blood have been lost. It is also realized that these groups of cases comprise sufficient numbers and that the use of